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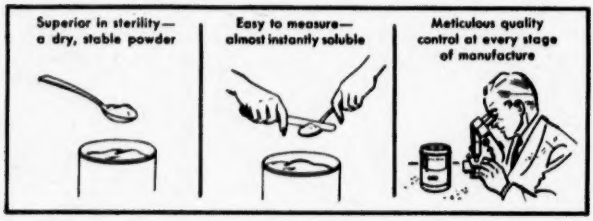

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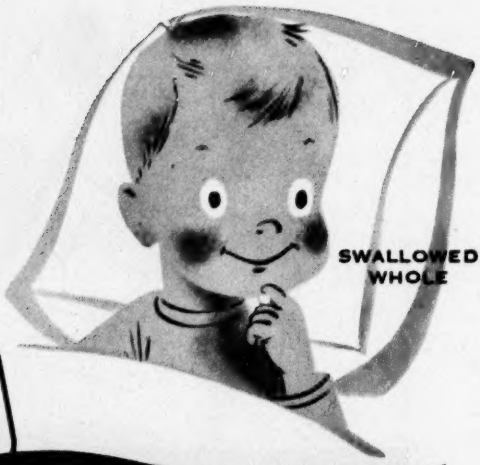

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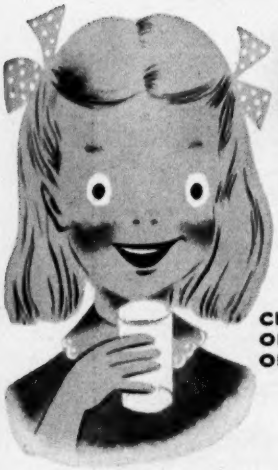

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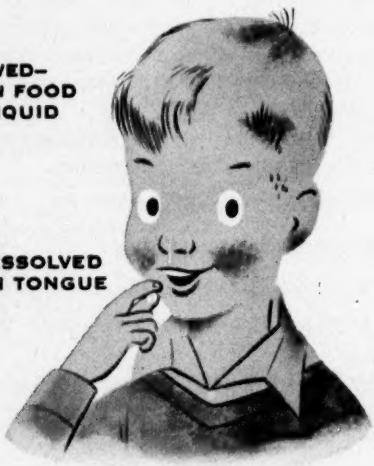

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*Journal of Pediatrics *39: 325 1951*
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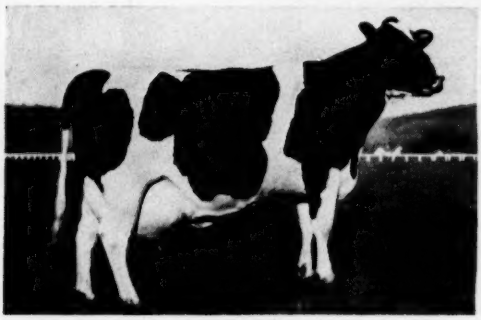

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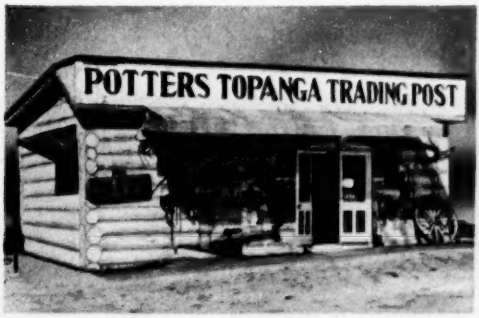

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J. Am. Dietet. A. 28:718, 1952.

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J. Pediat. 39:325, 1951.

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J.A.M.A. 146:35, 1951.

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Current Therapy 1952, p. 190.

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A Textbook of Oral Hygiene & Preventive Dentistry, 1950, chap. 6.

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This booklet again emphasizes the valuable application of meat in the dietary management of cardiac disease, hypertension, and obesity. Since, as the manual emphasizes, infectious diseases and such scourges as typhoid fever have now been controlled with antibiotics, chemotherapeutic agents and modern sanitation, "many physicians and scientists consider nutrition the most important environmental factor in health."

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*Food for Your Heart, a Manual for Patient and Physician, Department of Nutrition, Harvard School of Public Health, Harvard University, The American Heart Association, Inc., New York, 1952. Copies available through local Heart Association.

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American Journal of Diseases of Children

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USE OF CORTISONE AND CORTICOTROPIN (ACTH) IN TREATMENT OF RETICULOENDOTHELIOSIS IN CHILDREN

MURRAY H. BASS, M.D.
SAMUEL O. SAPIN, M.D.
AND
HORACE L. HODES, M.D.
NEW YORK

HAVING had the opportunity during the past three years of observing five children suffering from reticuloendotheliosis, we here wish to report the effect of corticotropin (ACTH) and cortisone on the course of this disease.

There has lately been renewed interest in the subject of reticuloendotheliosis in childhood, chiefly because a benign form of the disease, eosinophilic granuloma, has been described and shown to be related to previously-known clinical syndromes characterized by a much more serious prognosis.[1] We refer to Hand-Schüller-Christian disease and the rarer Letterer-Siwe disease.[2] It is not our purpose here to discuss at length the relationship of these three diseases; suffice it to say that there are now enough clinical descriptions of cases to warrant considering these diseases as due to the same underlying pathological process.[3] There is still doubt in the minds of some as to this relationship,[4] but the majority of pathologists and clinicians are agreed that eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease are not only related, but that they may even be stages in a single disease process. Eosinophilic granuloma,[4] which at first was described as a solitary lesion, is now known also to occur in multiple foci at the same time. Even when the lesions are multiple, the outlook in this condition is good. One of us (M. H. B.) has under observation a girl, now aged 11 years, in whom at the age of 2 years bone lesions developed which on biopsy proved to be eosinophilic

From the Pediatric Service of the Mount Sinai Hospital.

Presented before the section of pediatrics of the New York Academy of Medicine, Dec. 13, 1951.

1. Green, W. T., and Farber, S.: New England J. Med. **224**:832, 1941. Lichtenstein, L., and Jaffe, H. L.: Am. J. Path. **16**:595, 1940. Bass, M. H.: Am. J. Dis. Child. **61**:1254, 1941. Otani, S., and Ehrlich, J. C.: Am. J. Path. **16**:479, 1940.

2. Hand, A., Jr.: Tr. Path. Soc. Philadelphia **16**:282, 1893. Schüller, A.: Fortschr. Geb. Röntgenstrahlen **23**:12, 1915. Christian, H. A., in Contributions to Medical and Biological Research Dedicated to Sir William Osler, New York, Paul B. Hoeber, 1919, Vol. 1, p. 390. Letterer, E.: Frankfurt. Ztschr. Path. **30**:377, 1924. Siwe, S.: Ztschr. Kinderh. **55**:212, 1933.

3. Wallgren, A.: Am. J. Dis. Child. **60**:471, 1940. Gross, P., and Jacox, H. W.: Am. J. M. Sc. **203**:673, 1942. Green, W. T., and Farber, S.: J. Bone & Joint Surg. **24**:499, 1942. Jaffe, H. L., and Lichtenstein, L.: Arch. Path. **37**:99, 1944.

4. Siwe, S., in Advances in Pediatrics, editors, S. Z. Levine and others, New York, Interscience Publishers, Inc. **4**:117, 1949.

granuloma in the frontal and temporal bones, the mandible, the dorsal spine, the ileum, the humerus, and a rib. New bone lesions kept appearing for a period of three years. She was treated with x-ray only, and although her sixth dorsal vertebra has completely collapsed, she has had no symptoms referable to her illness during the past six years and is at the present time in excellent health.

Hand-Schüller-Christian disease was at first thought to be characterized by the following triad of symptoms: bony skull defects, diabetes insipidus, and proptosis.[3] It was gradually realized, however, that this clinical picture was present only in certain cases due to bone lesions in the vault and the base of the skull. It is now common knowledge that the disease is a general one, and that the lymph nodes, the spleen, the liver, the lungs, the skin, and the entire skeleton may be affected. The symptomatology and the course of this form of reticuloendotheliosis are so varied that it is very difficult to predict the outcome in any particular case. Children occasionally recover, may die from intercurrent disease, or may go on to the severe form of illness resembling Letterer-Siwe disease.

Letterer-Siwe disease is the most acute form of reticuloendotheliosis. It is regularly fatal, occurring in infancy with an acute onset resembling an infection, usually accompanied by fever, severe anemia, and cutaneous hemorrhages. There is marked hepatosplenomegaly, and the lymph nodes are greatly enlarged. The skin is dry with an eczematous eruption, often accompanied by papules and petechiae. The bone marrow is involved, and rarefactions in the bones may be present. The duration is short, the infant rarely surviving more than a few months and in some cases succumbing in a few weeks. This disease has been considered not to be familial, but one of us (M. H. B.) has observed a family in which three children born successively to the same parents died in early infancy with typical symptoms and pathological findings of Letterer-Siwe disease.

Treatment of the reticuloendotheliosis has consisted of the use of x-ray therapy and the antifolic acid drugs, besides symptomatic remedies such as iron and transfusions. In a disease process so diverse in its clinical manifestations and so varied in its prognosis, it is particularly difficult to judge correctly the value of any therapeutic agent, yet it is believed that x-ray is useful in healing eosinophilic granulomas and that antifolic acid preparations have a definite place in the treatment of Hand-Schüller-Christian disease. For the acute rapidly progressive syndrome described as Letterer-Siwe disease, no treatment has so far seemed to be of any avail.

REPORT OF CASES

CASE 1.—F. Z.,[5] a white boy, was well except for several of the usual childhood illnesses until October, 1949, when, at the age of 8 years, progressively enlarging retromandibular and preauricular nodes developed (Chart 1). The skin over these became purplish in color, then ulcerated and began to drain. In December, 1949, x-rays revealed several nodular lung infiltrations. At this time, biopsy of an occipital lymph node revealed the presence of a histiocytic granuloma. There was little lipoid material and a few eosinophiles. The histological picture was that seen in Hand-Schüller-Christian disease.

The boy was referred to the Mount Sinai Hospital, where he was treated with radiotherapy to the lungs and the lymph nodes under the direction of Dr. William Harris. He was also given a dose of P^{32} without effect. The liver and spleen began to enlarge. Four doses of 2 mg. of nitrogen mustard were administered intravenously, resulting in only a moderate decrease in the

5. Patient referred by Dr. Stephen Musliner.

size of the lymph nodes. Repeated courses of x-ray therapy were given, and finally the nodes stopped draining and decreased in size. However, the lesions in the lungs became worse, and the liver and spleen grew larger. In June, polyuria and polydipsia developed. The patient began to feel and look sicker. The liver was enlarged to 4 cm. below the costal margin. At this time he was given a tracer dose of 20 μc of P^{32}, and measurements revealed no increased uptake of the phosphorus by the body. He was therefore given 50 mg. of corticotropin administered intramuscularly daily for seven days followed by another tracer dose of P^{32}. The latter revealed evidence, this time, of increased uptake of the phosphorus, and therefore the boy was given corticotropin for two days followed by a therapeutic dose of 3 mc. of P^{32}. Despite this therapy, the downhill course continued with progression of the lung infiltration. Slight jaundice appeared in October, 1950, at which time the boy was given 100 mg. of cortisone by intramuscular administration daily for six days. After two days of cortisone treatment, a therapeutic dose of 3 mc. of P^{32} was again given. There was, however, no improvement, and the boy became worse.

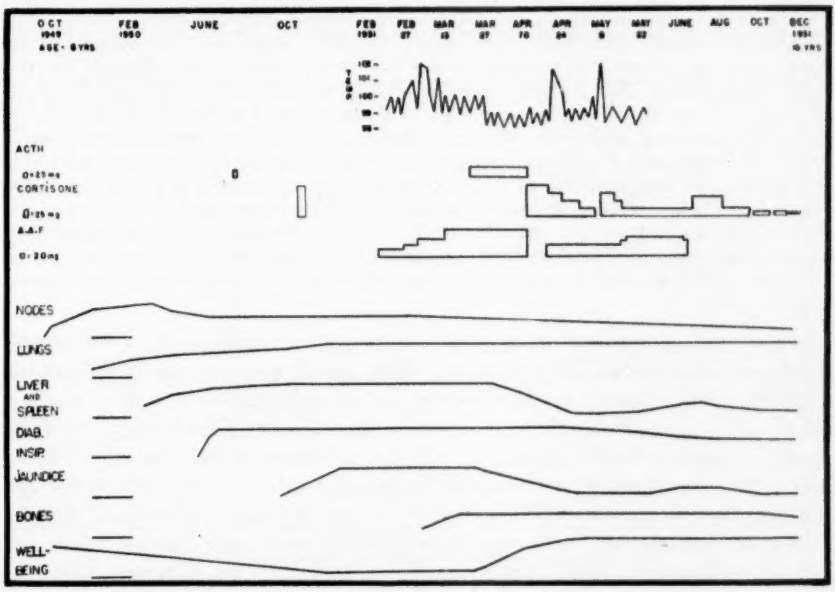

Chart 1 (Case 1).—Clinical course of patient.

In February, 1951, the child was readmitted to the hospital appearing gravely ill, extremely emaciated, and quite jaundiced. There were moderate generalized glandular enlargement and dullness with diminished breath sounds over the right chest. The liver was enlarged down to the umbilicus, and the spleen edge was 3 cm. below the costal border. There were dilated veins over the abdominal and chest walls. Xanthelasma was present on the eyelids, and several yellowish-brown macules were on the abdominal wall.

Laboratory studies revealed the following: hemoglobin, 13 gm. per 100 cc., white blood cell count, 15,000; differential count, a moderate shift to the left; erythrocyte sedimentation rate (Westergren), 125 mm. in one hour; albumin-globulin ratio, 2.4/4.7 per 100 cc. There was evidence of an obstructive type of jaundice; serum bilirubin, 2.5 mg. per 100 cc.; urine, 3+ reaction for bile; serum cholesterol, 685 mg. per 100 cc.; cholesterol esters, 380 mg. per 100 cc.; alkaline phosphatase, 88 King-Armstrong units; cephalin flocculation, 1+. X-rays revealed extensive bilateral lung infiltrations and pleural effusions. For the first time, x-ray showed cystic lesions in the mandible and the right pubic bone.

The patient was given 40 mg. of amino-an-fol (4-aminopteroylaspartic acid) daily, and this dose was gradually increased to 120 mg. daily without developing toxicity. On this regimen

there was persistent low-grade fever, the obstructive jaundice increased, and the boy appeared sicker. The urine output was 3 to 4 liters per day. He was, therefore, started on 60 mg. of corticotropin daily in four divided doses administered intramuscularly in addition to the amino-an-fol. With corticotropin his temperature fell to normal, his appetite, appearance, and behavior strikingly improved, and he started to walk about the ward. The jaundice subsided markedly, and the blood chemistry values returned toward normal. The liver and spleen decreased in size. The diabetes insipidus did not improve. A small pneumothorax appeared on the right but cleared without causing any difficulty.

Stomatitis appeared after three weeks of corticotropin and amino-an-fol therapy, and use of the latter was temporarily stopped. At this time treatment was changed from administration of corticotropin to 100 mg. of cortisone daily in four divided doses orally. This dosage was gradually lowered to 25 mg. daily, and after four weeks cortisone was discontinued. However, fever and jaundice promptly reappeared, and cortisone in doses of 75 mg. daily was again given, after which the temperature fell to normal, and the jaundice disappeared.

During this period of corticotropin and cortisone therapy the general appearance and sense of well-being showed extraordinary improvement. The lymph nodes, liver, and spleen progressively decreased in size. The diabetes insipidus was perhaps only slightly improved, but the jaundice disappeared. The chest and bone lesions as seen on x-ray, although no worse, were not improved. The patient was discharged in May, 1951, and instructed to take 25 mg. of cortisone and 100 mg. of amino-an-fol daily. After one month at home, the liver again became enlarged, and icterus reappeared. For this reason the cortisone dosage was increased to 50 mg. daily, and the amino-an-fol was discontinued. With this larger dose the jaundice and liver size again diminished. On two occasions thereafter cortisone was discontinued. Each time, within a few days, the boy began to feel sick and to have fever, anorexia, and nausea. With the reinstitution of cortisone therapy, 12.5 mg. daily, these symptoms promptly subsided. At the present time, on a regimen of 12.5 mg. of cortisone every other day, the patient is normally active, attends school, and feels well.[6]

Summary.—An 8-year-old boy was suffering from a severe type of reticuloendotheliosis involving lymph nodes, lungs, liver, spleen, and bone and from diabetes insipidus. After treatment with corticotropin and cortisone, he is now, at the age of 10 years, symptomatically well. Corticotropin and cortisone brought the temperature down to normal, produced a marked improvement in the sense of well-being and appetite, and caused shrinking of the lymph nodes, liver, and spleen and the disappearance of jaundice. The pulmonary lesions, although not worse as seen on x-ray, did not improve. The bone lesions, similarly, did not improve. The diabetes insipidus was slightly improved. Amino-an-fol did not effect any improvement when it was administered alone, albeit maximum dosage to the point of toxicity was not reached during this period. Thereafter the drug was used along with corticotropin and cortisone, and its exact effect cannot be estimated.

Case 2.—P. C., a white girl, had been well except for upper respiratory infections when she became ill in February, 1948, at the age of 5 years, with intermittent fever, generalized lymphadenopathy, and joint pains (Chart 2). In February, 1949, one year after the onset of her symptoms, multiple joint swelling with high fever developed and she was thought to have Still's disease. The joints gradually improved, but the fever and lymph node enlargement persisted. Difficulty in hearing also developed, and the patient began to limp. Roentgenograms of the left foot revealed a suggestion of a lytic lesion in the cuboid bone. In January, 1950, a lymph node biopsy was performed, and the histological picture revealed a histiocytic granuloma with many foam cells and eosinophiles characteristic of Hand-Schüller-Christian disease.

6. Four months after this case was presented the boy again began to feel ill, and the pulmonary infiltration increased rapidly, though no new bone lesions appeared. He was hospitalized and treated with antifolic drugs, but went downhill rapidly and died on May 21, 1952.

The patient was referred to the Mount Sinai Hospital in February, 1950, at the age of 7 years. She appeared somewhat underweight and chronically ill. The positive physical findings consisted of moderate generalized glandular enlargement, a spleen enlarged to 3 cm. below the costal margin, and a moderate degree of bilateral nerve-type deafness. The blood cell count and the urine and blood chemistry, including cholesterol and esters, were normal. X-rays revealed multiple cystic lesions in the left humerus, both tibiae, and the left ulna.

In the hospital, the patient's temperature fell spontaneously. Intramuscular administration of cortisone was then started with a dosage of 100 mg. daily for 10 days. On this therapy the patient symptomatically was better, and the lymph nodes and spleen began to decrease in size. The bone lesions did not improve. One week after cortisone therapy was stopped the patient again began to look and feel sick, and her temperature rose to 101.5 F., though the nodes and spleen did not enlarge. Cortisone was again given in doses of 100 mg. administered intramuscularly daily for one week. With this medication the patient again felt well, her temperature became normal, and her appetite improved. The bone lesions showed some extension during this time. Cortisone therapy was stopped, and five days later fever and toxicity reappeared. The fever, temperature as high as 104 F., lasted about two weeks, despite acetylsalicylic acid therapy.

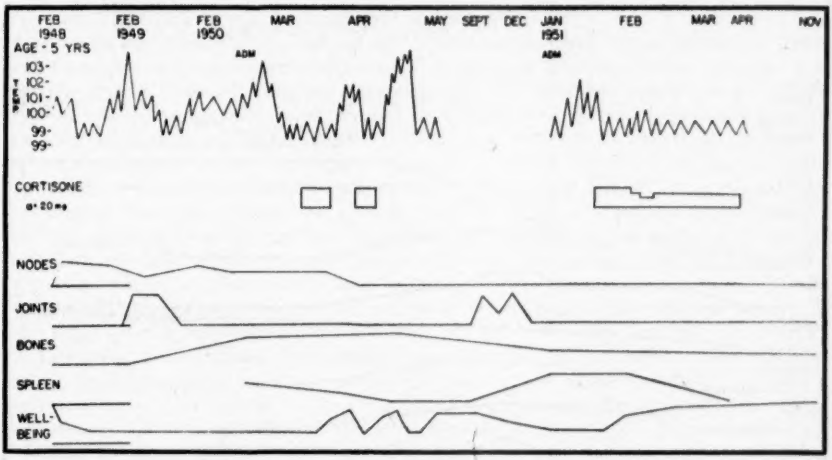

Chart 2 (Case 2).—Clinical course of patient.

Finally the temperature fell to normal. The girl felt somewhat improved and was discharged in May, 1950. There were no untoward effects resulting from the cortisone, except for the development of a moon facies.

At home, she did fairly well for four months, but then had a bout of arthritis involving the right wrist. This cleared spontaneously, but low-grade fever reappeared, she again felt sick, and she was readmitted to the hospital in January, 1951.

At this time the patient appeared in no acute distress, but again had a spleen enlarged to 2 cm. below the costal border. There was marked bilateral deafness involving both bone and nerve conduction. The lymph nodes were still normal in size. The blood cell counts, urine, and blood chemistry, including cholesterol and esters, were normal. The erythrocyte sedimentation rate (Westergren) was 70 mm. in one hour. X-rays revealed considerable healing of many of the previously-noted bone lesions.

Cortisone treatment was begun in a dosage of 100 mg. by oral administration in four divided doses per day. Again the patient felt and looked better, and her temperature became normal. The spleen shrank to normal size. The erythrocyte sedimentation rate fell to 26 mm. in one hour. The cortisone dose was lowered to 50 mg. daily, but the erythrocyte sedimentation rate rose. The cortisone dose was increased to 75 mg. daily, and with this dose the erythrocyte sedimentation rate became normal. The patient was then discharged to be maintained on 75 mg.

of cortisone daily at home, and this was continued until April, 1951, for a total of 2½ months. There was no obvious untoward effect during this time. Since then no medication has been given, and there has been steady improvement.

Summary.—A girl, 5 years of age at the onset of her disease, exhibited generalized adenopathy, fever, and multiple joint swellings. After a year bone lesions appeared, and a biopsy proved the condition to be reticuloendotheliosis. The patient was treated with cortisone for several courses and now, three years after the onset, looks and feels perfectly well. The physical findings are unremarkable except for the persistent deafness, the etiology of which is still unexplained. No

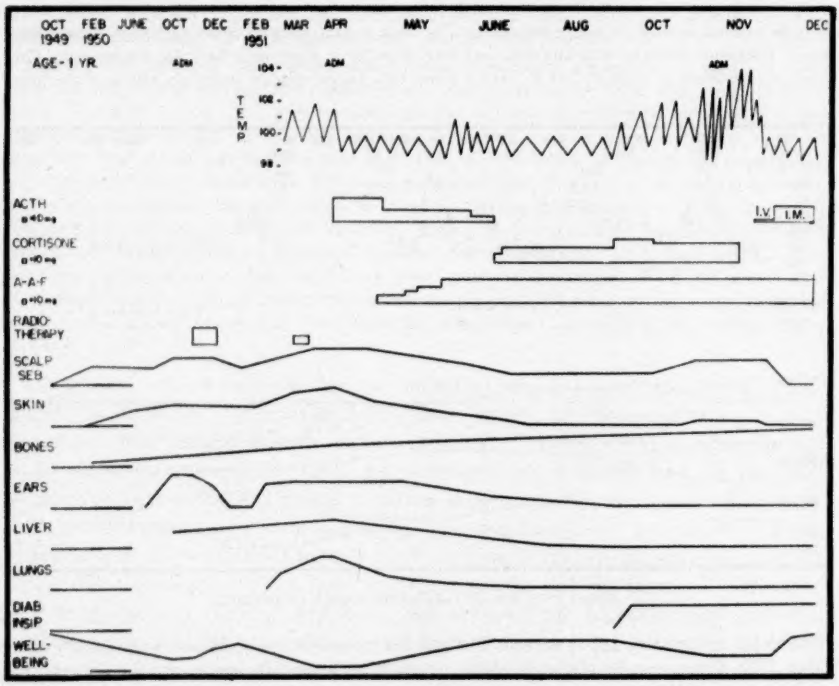

Chart 3 (Case 3).—Clinical course of patient.

ear discharge or mastoid bone lesions were ever noted. X-rays of the long bones have shown continued healing. Whether or not this is the direct result of the administration of cortisone, we are unable to say. On the other hand, cortisone definitely stopped the fever and produced a feeling of well-being, at the same time causing disappearance of lymphadenopathy and splenomegaly. We are unable to say whether this disease is cured or whether there may be a relapse at some future time.

CASE 3.—E. S., a white girl, was well, except for several episodes of bronchitis, until October, 1949, when at 1 year of age a persistent seborrheic dermatitis of the scalp developed (Chart 3). Six months later she began to drool, her teeth erupted prematurely, and her gums became inflamed. In August, 1950, bilateral purulent otitis media developed, which was resistant to antibiotics. X-rays of the mastoids were taken, and cystic lesions in the skull were discovered.

The patient was referred to the Mount Sinai Hospital in October, 1950, for the first time. Physical examination revealed a 2-year-old child appearing chronically ill. There was a generalized scaling brawny eruption of the skin and scalp. There were palpable bony defects of the skull and the right mastoid process. The right ear was draining pus, and a granulomatous mass filled part of the canal. The gums were spongy, and there were several loose incisor teeth; the lower six-year molars, surprisingly enough, had already erupted. The liver was 2 cm. below the rib cage, and the spleen was just palpable.

Blood cell counts, urinalyses, blood chemistry, including cholesterol and esters, and total lipids were all normal. X-ray revealed numerous multiple bony defects in the skull, mandible, and left femur.

Biopsies of the femur, gum, and skin lesions all revealed a histiocytic granuloma, with foci of lipidization and many eosinophiles, interpreted as characteristic of Hand-Schüller-Christian disease.

A course of x-ray therapy was given: 600 r (air) to the right side of the head and mandible, 600 r (air) to the left mandible, and 600 r (air) to the left femur lesion. The mastoid and femur defects then began to show signs of healing clinically and on x-ray. The right ear discharge ceased, and the granuloma in the canal became much smaller. The patient was slightly improved symptomatically, and she was discharged in December, 1950.

While at home, serial x-rays revealed healing of the defect in the femur, on which a biopsy had been done, and it was then treated with x-ray therapy. The skull lesions, however, progressed. Another course of x-ray therapy was given to the skull, but without effect. The girl showed weight loss, anorexia, cough, dyspnea, and fever. The right ear again began to drain, the skin and scalp became worse, and the child was readmitted to the hospital in April, 1951, after four months at home.

She appeared severely, acutely, and chronically ill. There were dyspnea and orthopnea, with suprasternal retractions. There was alopecia, and there were also palpable skull defects, a purulent discharge from the right ear, hyperplasia of the gums, medium moist rales over the left chest, and diminished breath sounds on the right side. The liver edge was felt 3 cm. below the costal margin. A right exophthalmos was now evident. The rash was generalized and striking. It consisted of brawny induration with erythema and desquamation and papules up to 4 mm. in size. There were scattered petechiae. The palms and soles were also involved.

Laboratory studies revealed the following: hemoglobin, 9.5 gm. per 100 cc.; white blood cell count, 10,600; differential count, a moderate shift to the left; platelets, 135,000; erythrocyte sedimentation rate, 24 mm. in one hour. The chest x-ray showed diffuse linear and nodular infiltrations in both lungs. Bone x-rays revealed widespread destructive lesions in the skull, ribs, long bones, and mandible.

The patient at this time was critically ill and presented the clinical picture of Letterer-Siwe disease in its terminal phase. Intramuscular administration of 60 mg. of corticotropin daily in four divided doses was begun on admission. The temperature rapidly fell to normal. The skin and scalp lesions began to clear. The liver became smaller. Dyspnea disappeared, and clinically the patient became gradually happier, more alert, and her appetite increased considerably. The bone lesions did not improve. During the second hospital week, the child developed a right-sided pneumothorax, with mediastinal and subcutaneous emphysema. There was a temporary increase in dyspnea, but the emphysema and pneumothorax cleared spontaneously.

After two weeks of corticotropin treatment, amino-an-fol was added, starting with a dose of 20 mg. and increasing to 60 mg. daily. The corticotropin dose was decreased to 30 mg. daily. After 2 months of corticotropin treatment and 1½ months of amino-an-fol the patient appeared playful and very alert and was eating very well. Her skin was almost normal. The seborrhea of the scalp was improved, but still present. The hair had grown in again. The lungs were clear on physical examination and the liver much smaller. The ear drainage was considerably less. X-rays revealed considerable clearing of the lung lesions, but the bones showed progressive involvement. The hemoglobin value rose to 13 gm. per 100 cc. without transfusion, and the erythrocyte sedimentation rate became normal.

The medication was then changed from corticotropin to cortisone, 37 mg. administered orally daily in four divided doses, and amino-an-fol treatment was continued. The child was discharged while still taking these two drugs in June, 1951, remarkably improved.

Three months later she again began to go downhill. She developed, for the first time, polyuria and polydipsia. Fever reappeared, the scalp became worse, the rash on the body reappeared, though in a milder form, and the bone lesions progressed. However, the ear discharge ceased, the lungs remained clear, and the liver did not enlarge again. The dose of cortisone was increased to 60 mg. daily, but without effect. The patient was therefore readmitted for the third time in October, 1951. She appeared moderately ill, though not as acutely as on her second admission, six months previously. There was a moon facies. The exophthalmos was unchanged; the ears were no longer draining. The scalp presented a moderately severe seborrhea and the trunk a mild erythematous papular eruption. The skull defects were easily felt. There were several loose incisors. There were definite polyuria and polydypsia, with a maximum urinary specific gravity of 1.016 following a salt-loading test. X-rays revealed the lungs to be clear, but showed further extension of the bone lesions.

In the hospital, the patient ran a spiking fever and became more toxic; it was decided to stop use of cortisone, to continue amino-an-fol, and to give corticotropin intravenously. Accordingly, she was given 8 mg. of corticotropin by vein over an eight-hour period daily for a total of nine days. Following this she was maintained on 40 mg. of corticotropin administered intramuscularly daily. On this regimen the temperature promptly fell to normal. The patient became happy and playful, with an excellent appetite. After one month of therapy she seemed like an entirely different child, running about the ward. The seborrhea of the scalp cleared completely for the first time in two years. The skin also cleared. The bones remained unchanged. After one month of corticotropin therapy, the urine concentrated to a maximum specific gravity of 1.027. However, the polyuria and polydipsia remained. The patient is still in the hospital, medication has been changed from corticotropin to orally administered cortisone, and an attempt is being made to adjust the dose of cortisone and also to increase the dose of amino-an-fol to the point of toxicity to see if the progression of the bone lesions can be halted.

Summary.—In a one-year-old baby girl there developed seborrhea, eczematoid skin lesions, bone defects, ear discharge, hepatomegaly, lung lesions, and diabetes insipidus. Bone and skin biopsies revealed reticuloendotheliosis. The disease ran a very severe course, with emaciation and high fever; petechial skin lesions developed, and she appeared moribund. Corticotropin and cortisone aided in producing the following changes: (1) a striking remission of fever, (2) a marked improvement in the state of well-being and appetite, (3) a clearing of skin and scalp lesions, (4) an improvement in the ear lesions, (5) a decrease in the size of the liver, (6) a clearing of lung lesions, and (7) possible improvement in the diabetes insipidus. The bone lesions, unfortunately, were not improved and, indeed, progressed during therapy. No toxicity was noted from the prolonged administration of the steroid hormones. A moon facies developed, and some euphoria was present. Amino-an-fol was also administered to this child, but its role in effecting her improvement is not clear, since it was given in conjunction with the hormones, and the dosage was not pushed to toxic levels. Two and one-half years after the onset, the child's condition is good, though the final outcome cannot be foretold.

Case 4.—N. G.,[7] a white boy, except for an episode of bronchitis in infancy, was perfectly well until September, 1948, when, at 3 years of age, a generalized macular erythematous eruption developed (Chart 4). This cleared after one month, only to recur several times. Nine months after the onset of the rash one ankle became swollen and painful. On another occasion the fingers and wrists became inflamed. In December, 1949, fever developed, and inflammation of the ankle again developed.

He was admitted to the Mount Sinai Hospital at this time and presented the appearance of a chronically ill child, with evidence of considerable weight loss. There was slight enlargement of all the lymph nodes. The abdomen was distended, the liver was enlarged to 2.5 cm.

7. Patient of Dr. Carl Zelson.

below the costal margin, and the spleen was slightly enlarged. A generalized macular erythematous rash which involved the palms and soles was present. The wrists were swollen and tender.

Laboratory studies revealed the following: hemoglobin, 10 gm. per 100 cc.; white blood cell count, 4,500; differential count, a considerable shift to the left; erythrocyte sedimentation rate, 70 mm. in one hour; values on urinalysis, normal; blood chemistry and cultures, normal. X-rays of the chest and bones and other studies showed significant abnormalities.

In the hospital, the temperature was of the remittent septic type despite the use of antibiotics. The lymph nodes, spleen, and liver became progressively larger, and the patient appeared more toxic. A biopsy was then done on an axillary lymph node. The microscopic appearance was that of a histiocytic proliferation without the presence of foam cells, considered by the pathologists to be compatible with a diagnosis of Hand-Schüller-Christian disease.

The patient was started on a regimen of 60 mg. of cortisone administered intramuscularly daily. On this therapy the boy improved symptomatically; his temperature fell, his rash cleared, the joint swelling disappeared, and the lymph nodes, the liver, and the spleen became smaller. Because of rapid weight gain, cortisone therapy was stopped after five days. Fever and toxicity promptly returned. The rash and joint swelling reappeared. The lymph nodes became larger.

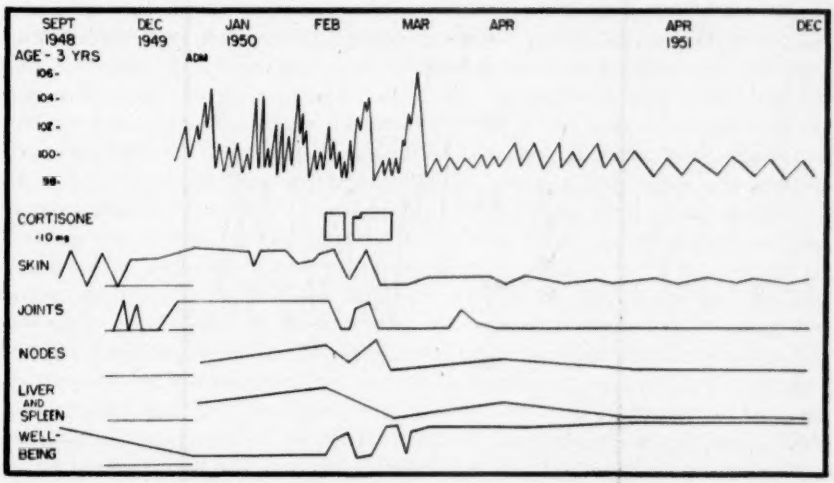

Chart 4 (Case 4).—Clinical course of patient.

A dose of 50 mg. of cortisone administered intramuscularly daily was again given, then increased to 60 mg. daily. After four days the fever, rash, and joint swelling again vanished, and there was marked symptomatic improvement. The lymph nodes again decreased in size. The supply of cortisone gave out after one week of therapy. The temperature promptly rose, and a vesicular eruption appeared, which proved to be varicella. After five days the fever disappeared. There was no recurrence of the original rash or arthritis during the course of the varicella. However, in the latter part of March, three weeks after cortisone therapy, the boy again exhibited the macular erythematous eruption, though only on the extremities. The lymph nodes and the spleen increased in size, and the left wrist became transiently inflamed. He appeared only mildly ill and was sent home in April, 1950.

At home, on no specific therapy, there was low-grade fever along with evanescent macular erythematous lesions on the lower extremities for about a year. However, the spleen, liver, and lymph nodes gradually reverted to normal size, and the joints remained normal.

In the past nine months the boy has been afebrile, has felt perfectly well, and has gone to school. At present except for a few macular erythematous lesions several millimeters in size on the lower extremities the physical examination shows no significant abnormalities. Recent x-rays show the chest and bones to be normal.

Summary.—A 3-year-old boy had a macular erythematous eruption followed by joint swellings, fever, lymphadenopathy, and hepatosplenomegaly. Lymph-node biopsy revealed a reticuloendothelial proliferation. Cortisone was given for two relatively short periods and each time produced a marked feeling of well-being, stopped the fever, cleared the rash and joint inflammation, and reduced the size of the lymph nodes, liver, and spleen. Following the cortisone treatment the symptoms recurred, though to a much milder degree. Thereafter the patient progressively improved and now, 3½ years after the onset, is apparently well.

CASE 5.—G. W., a white baby boy, was admitted to the Mount Sinai Hospital on April 26, 1951, at 3 months of age (Chart 5). He was well until 10 days before admission, when fever,

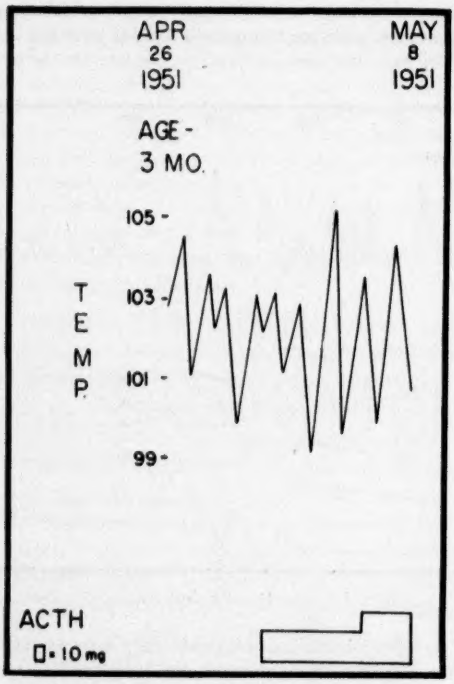

Chart 5 (Case 5).—Clinical course of patient.

persistent cough, rash, and diarrhea developed. On admission he was an acutely ill infant, very pale and apathetic. The temperature was 103 F. There was a striking eruption consisting of generalized scaling and induration of the skin and scalp, with scattered petechiae and ecchymoses. There were hemorrhagic areas on the tonsils. The cervical and submandibular nodes were very large, firm, and matted. There were diminished breath sounds over the right chest and also marked hepatosplenomegaly.

Laboratory studies revealed the following: hemoglobin, 5.0 gm. per 100 cc.; white blood cell count, 11,000; differential count, a shift to the left; platelet count, 30,000; albumin-globulin ratio, 2.4/2.2 per 100 cc.; cholesterol, 95 mg. per 100 cc.; cholesterol esters, 37 mg. per 100 cc. A chest x-ray revealed nodular infiltrations in the left lung; bone x-rays were normal.

Skin and lymph node biopsies were performed, and sections showed nonlipid histiocytosis, characteristic of Letterer-Siwe disease.

The infant was given a transfusion, given antibiotics, and started on a regimen of 40 mg. of corticotropin administered intramuscularly daily in four divided doses. After four days this was increased to 60 mg. daily. Despite this therapy the septic temperature persisted. The white blood cell count rose to 40,000, and the platelet count fell to 10,000. Dyspnea developed, the course of the illness continued downhill, and the infant died after eight days of corticotropin therapy.

Postmortem examination revealed a diffuse nonlipid histiocytic infiltration involving the skin, lymph nodes, spleen, liver, lung, and bone marrow. There were also many petechial lesions on the skin, testes, epicardium, lungs, and intestinal mucosa.

Summary.—This was a severe and fulminating case of the acute form of reticuloendotheliosis (so-called Letterer-Siwe disease) in a 3-month-old infant. Corticotropin therapy completely failed to influence the course of the disease.

CONCLUSIONS

The histories of the five children described above lead us to believe that in cortisone and corticotropin we have a remedy, which, though not in itself curative, is of great value in the treatment of these diseases. In Case 5, that of the infant with Letterer-Siwe disease, corticotropin was of no value whatever. However, in Case 3, in which the clinical picture was that of severe Hand-Schüller-Christian disease passing into an acute phase in which all the symptoms were those seen in Letterer-Siwe disease, corticotropin proved to be of the greatest value. As in rheumatic fever, the symptoms of acute illness (lethargy, anorexia, fever, eruptions, bleeding tendency, swelling of lymph nodes and joints, splenomegaly and hepatomegaly) seemed miraculously to disappear, only to return when administration of the drug was stopped. In this child the intravenous administration of corticotropin was definitely lifesaving. It was purposely given in small doses (8 mg.) in intravenous dextrose solution by slow drip over a period of eight hours each day for nine days. This method of administration has been recommended as providing the best physiological stimulus to the adrenal glands. In the more chronic phase of the disease cortisone was used, and though in some instances it was necessary to administer it over a period of time, it, too, proved very useful. It would appear that both cortisone and corticotropin relieve the child of many subjective symptoms, thus permitting him to eat and sleep and thereby improving his nutrition and aiding him in combating the disease. We do not imply that cortisone or corticotropin cures children suffering from reticuloendothelial disease, but these drugs are extremely valuable adjuvants and should certainly be used along with other agents, such as the antifolic acid drugs or x-ray therapy.

The Pathology Department of the Mount Sinai Hospital made the studies of the pathological specimens obtained in each of the five cases. Dr. William Harris was responsible for the administration of radiotherapy.

ANGIOCARDIOGRAPHY IN CONGENITAL HEART DISEASE CORRELATED WITH CLINICAL AND AUTOPSY FINDINGS

A Five-Year Clinical and Pathological Study of Thirty-Four Cases in Infants and Young Children out of a Series of Eleven Hundred Patients, and Four Hundred Twenty-Five Angiocardiograms

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WHILE angiocardiography was first introduced in 1937 by Castellanos, Pereiras, and Garcia [1] and was perfected as a practical technique by Robb and Steinberg,[2] its widespread use as an aid to clinical diagnosis of congenital malformations of the heart has not come about until recent years. Much of the literature written concerning angiocardiography has been collected from studies on older children and adults. There have been few reports, however, in which predominantly infants and young children have been studied.[3] In their recent comprehensive review of the subject of angiocardiography, Dotter and Steinberg [4] reported that only 32 cases of congenital malformations of the heart of the cyanotic type had been reported prior to their publication in which angiocardiography had been performed and correlated with autopsy findings. It is, therefore, the purpose of this study to present a com-

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From the Hektoen Institute for Medical Research, the Pediatric Cardiophysiology Department of the Cook County Children's Hospital, and the Pediatric Department of the University of Illinois College of Medicine. Aided by a grant from the Jack Galter Foundation.

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plete clinical-pathologic correlation with angiocardiographic studies of 34 cases, 25 of which were in infants under one year of age. Twenty-two of these cases fall into the cyanotic group of congenital cardiac malformations.

MATERIAL STUDIED

Since the establishment of the pediatric cardiology department at the Cook County Children's Hospital in 1947, over 1,100 patients with congenital malformations of the heart have been studied, and over 425 angiocardiograms have been taken. Prior to July, 1950 we were using a handmade apparatus in which the cassettes were pushed through a tunnel beneath the surface of the table. By this method one film was taken approximately every second. However, the timing of this apparatus was inaccurate, thus limiting the value of the studies. Since July, 1950, we have been using the Fairchild camera which changes cassettes every one-half second. Usually about 20 views are taken on each angiocardiogram. One hundred thirty-five patients have been studied with a total of 195 angiocardiograms since the acquisition of the Fairchild camera. In our entire series of 425 angiocardiographic studies, one patient died following the second injection of iodopyracet (diodrast®) given one-half hour after the first injection, and another death occurred following the use of iodopyracet in retrograde arterial angiocardiography.[5] This publication deals only with patients who have come to autopsy during the past five years, the vast majority of them belonging to the cyanotic type.

The 34 cases studied may be classified into the following groups:

A. Cyanotic Group
   1. Complete transposition of the great vessels, 7 cases (Table 1)
   2. Tetralogy of Fallot, 5 cases (Table 2)
   3. Pseudotruncus communis, 2 cases (Table 3)
   4. Tricuspid atresia, 2 cases (Table 4)
   5. Ebstein's anomaly, 2 cases (Table 5)
   6. Tetralogy with interauricular septal defect, pentalogy, 2 cases (Table 6)
   7. Pulmonary stenosis with interauricular septal defect, 2 cases (Table 7)

B. Noncyanotic Group
   1. Persistent atrioventricularis communis, 1 case (Table 8)
   2. Interventricular septal defect, 2 cases (Table 9)
   3. Interventricular septal defect and interauricular septal defect combined, 4 cases (Table 10)
   4. Coarctation of aorta, 2 cases (Table 11)
   5. Endocardial fibroelastosis, 2 cases (Table 12)
   6. Eisenmenger's complex, 1 case (Table 13)

RESULTS OF THE STUDY

A. Cyanotic Group.—1. Complete Transposition of the Great Vessels (Table 1): This malformation consists anatomically of a complete reversal of the positions of the pulmonary artery and the aorta, the pulmonary artery coming completely off the left ventricle and the aorta off the right ventricle. Since it is obvious that life could not exist without a communication between the two systems, shunts through one or more of the following associated defects occur: patent foramen ovale, interauricular septal defect, interventricular septal defect, or patent ductus arteriosus. As seen in Table 1, the following defects were found in the seven cases of complete transposition studied: (*a*) single ventricle, (*b*) patent foramen ovale and patent ductus, (*c*) pulmonary stenosis and one or more septal defects, (*d*) combined interauricular and interventricular septal defects, and (*e*) right aortic

5. Sodium iodomethamate (neoiopax®) was used in amounts of 1 to 1.5 cc. per kilogram of body weight in the last 195 angiocardiograms.

TABLE 1.—*Complete Transposition of Great Vessels*

Case	Age at Death, Mo.	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Surgery	Autopsy Findings
1	6	Complete transposition with right aortic arch	Marked cyanosis at birth; early progressive cardiac failure; oxygen saturation 72%; increased vascular pulmonary pulsations and right aortic arch; ECG showed progressive right ventricular hypertrophy, also right auricular hypertrophy	Anteroposterior: superior vena cava pushed to right; dense aorta and small pulmonary artery seen at 1½ sec.; dye from right auricle into left auricle; right aortic arch; dye still in heart at 10 sec.	0	Markedly enlarged heart; complete transposition of great vessels; single ventricle; pulmonary stenosis; patent ductus arteriosus; right aortic arch; closed foramen ovale
2	3	Complete transposition with pulmonary stenosis	Cyanosis since birth; marked cardiac enlargement; systolic murmur at base; narrow base; right ventricular hypertrophy; decreased pulmonary pulsations; ECG showed right heart strain	Anteroposterior: transposed aorta seen at 1 sec.; light pulmonary artery at 2 sec.; marked dilatation of right auricle and right ventricle; dye gone by 5 sec.	Exploratory; died same night	Markedly enlarged heart; complete transposition; patent ductus arteriosus; patent foramen ovale; right ventricular hypertrophy and dilatation
3	3	Complete transposition	Marked cyanosis since 6 wk.; soft systolic murmur in left 3d interspace; enlarged heart with narrow base and enlarged right auricle, right ventricle, and left ventricle; ECG showed no axis deviation	Anteroposterior: transposed aorta and light pulmonary artery seen at 1 sec.; little dye in lungs; dye gone from heart by 5 sec.	0	Single ventricle; mitral stenosis; patent ductus arteriosus; patent foramen ovale; transposition of great vessels
4	5	Complete transposition	Cyanotic attacks; soft systolic murmur; very large heart with narrow base; large right auricle and right ventricle; increased pulmonary vascular markings; ECG showed combined ventricular hypertrophy	Posteroanterior: dense transposed aorta and light pulmonary artery on Film 1 (1 or 2 sec.); moderate amount of dye in lungs; large pulmonary artery and right ventricle; whole heart filled with dye on Film 4 (about 6 to 7 sec.)	0	Transposition of great vessels; large interventricular septal defect; patent foramen ovale; closed ductus botalli
5	3	Complete transposition with patent ductus arteriosus	Cyanosis at birth; rapid cardiac enlargement in first 6 wk.; narrow base with right ventricular and left ventricular enlargement; increased pulmonary vascular pulsations; ECG showed marked right auricular and right ventricular hypertrophy and left heart strain	Left antero-oblique: transposed dense aorta at 1 sec.; light pulmonary artery at 1½ sec.; wide aortic window; dye gone by 5 sec.	0	Transposition of great vessels; patent foramen ovale; small interventricular septal defect; ductus botalli almost closed; right ventricular hypertrophy
6	16	Common trunk	Cyanosis since birth; loud systolic murmur over precordium; markedly enlarged heart with concavity in pulmonary area; large right auricle, right ventricle, and left ventricle; ECG showed right heart strain with right auricular hypertrophy	Left antero-oblique: large dense aorta, small pulmonary artery on Film 1 (1 to 2 sec.); left auricle on Film 1 with interauricular septal defect; dye gone from heart by 10 sec.	0	Transposition of great vessels; interauricular septal defect; patent ductus arteriosus; marked enlargement of right ventricle
7	2	Complete transposition with pulmonary stenosis	Cyanosis since birth; Grade IV systolic murmur; marked cardiac enlargement with large right auricle and right ventricle; also large left ventricle; diminished pulmonary vascular pulsations	Left antero-oblique: transposed aorta at 1½ sec.; small pulmonary artery at 2 sec.; wide aortic window; large right auricle and right ventricle; dye gone from heart by 5 sec.	0	Markedly enlarged heart; transposition of great vessels; pulmonary stenosis; patent foramen ovale; patent ductus arteriosus; marked right ventricular hypertrophy

arch and septal defects. While the prognosis in complete transposition is uniformly fatal, the length of life depends upon the amount of blood shunted between the two circulations; the greater the total shunt, the better the prognosis.

As seen in Table 1, the main features of this anomaly may be as follows: 1. There is moderate to marked cyanosis at birth. 2. Roentgenograms reveal a rapidly enlarging heart in the first weeks of life. The configuration of the heart is usually globular with a narrow base in the posteroanterior view, becoming wider in the oblique view, and there is usually a concavity in the pulmonary area. 3. Fluoroscopy reveals normal or exaggerated pulmonary vascular pulsations unless there

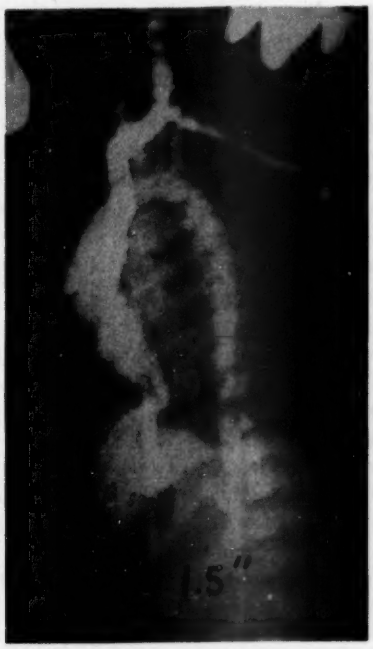

Fig. 1 (Case 5).—Complete transposition of the great vessels. At 1½ seconds the aortic arch makes a wide sweep, and there is no pulmonary artery visible.

is an associated pulmonary stenosis (Case 7). 4. Auscultation of the heart reveals no characteristic murmur. Variation from no murmur to a loud systolic murmur may occur. The second pulmonic sound is normal to accentuated in intensity unless there is an associated pulmonary stenosis, in which case it may be diminished. 5. Electrocardiograms usually show marked right ventricular hypertrophy, and perhaps right auricular hypertrophy as well. In Cases 4 and 5 combined right and left ventricular hypertrophy was present. This may possibly be explained by the fact that both had associated defects permitting large shunts of blood back and forth between the two circulations. In Case 3 no axis deviation was shown on the electrocardiogram and a single ventricle was shown pathologically.

Angiocardiography presents the following characteristic features: 1. The aorta usually fills with dye directly from the right ventricle in 1 to 1½ seconds. The

pulmonary artery, if seen at all, will usually not fill until one-half to one second after the aorta, as dye must pass through either a patent ductus or a septal defect into the left side of the heart before it can visualize the pulmonary artery. The density of the pulmonary artery is much less than that of the aorta since relatively less dye enters it. In Cases 1 and 3, however, the aorta and pulmonary artery were visualized simultaneously, since there was a single ventricle. 2. In the left antero-oblique projection (Case 5, Fig. 1) the aortic arch makes a wide sweep because it takes off from the right ventricle. The pulmonary artery shows no communication with the right ventricle (Case 5, Fig. 1). 3. Dye empties from the heart rapidly, usually in five to six seconds, passing into the systemic circulation by way of the transposed aorta. It must be remembered that, although little dye is seen entering the lungs on the angiocardiogram, this does not indicate a diminished pulmonary blood flow due to pulmonary stenosis. The reason for this is that most of the dye is quickly carried off by the transposed aorta without being shunted into the pulmonary circulation. The only angiocardiographic indication of an associated pulmonary stenosis along with complete transposition may be the small caliber of the pulmonary artery (Cases 6 and 7). It is felt that the left antero-oblique projection is the best single view for angiocardiographic demonstration of complete transposition of the great vessels. It must also be remembered that angiocardiography will usually be of little value in determining which of the septal defects is present or whether a patent ductus is present.

2. Tetralogy of Fallot: Although the name of this anomaly implies four defects, the malformation actually consists of two basic defects, the other two stemming from these. The two basic defects are pulmonary stenosis and dextroposition of the aorta. The two related defects are interventricular septal defect, which must necessarily accompany the overriding aorta, and the right ventricular hypertrophy which results from both basic defects. The pulmonary stenosis may be infundibular or valvular in type, usually infundibular. The cause for cyanosis is that unoxygenated blood from the right ventricle enters the overriding aorta directly, and, therefore, less blood enters the pulmonary circulation. Hence, the greater the degree of dextroposition of the aorta, in general, the greater the cyanosis and the more severe the entire clinical picture.

The five cases presented here (Table 2) show interesting pathological variations in severity of the disease. Case 9 (the oldest patient, aged 10 years) presented a rather characteristic clinical picture for the tetralogy of Fallot. Pathologically, there was a moderate degree of dextroposition of the aorta as well as a moderate degree of pulmonary infundibular stenosis. However, the pulmonary artery was of good size. Case 10 (the youngest patient, aged 3 weeks) presented the most extreme clinical picture. This was correlated pathologically with a marked degree of dextroposition of the aorta, along with an extreme degree of pulmonary stenosis, almost an atresia. In addition, there was stenosis of the left pulmonary artery, about 1.5 cm. in length.

The clinical features in the ordinary case of tetralogy of Fallot consist of the following: 1. Cyanosis may be present or absent at birth. If absent, it may begin at any time, usually during the first year of life. The earlier and severer the cyanosis, the graver the prognosis, in general. 2. Dyspnea and cyanosis increase on exertion. 3. A moderate to loud systolic murmur is heard over the pulmonary area and the left parasternal region. The second pulmonic sound is usually dimin-

TABLE 2.—*Tetralogy of Fallot*

Case	Age at Death	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Surgery	Autopsy Findings
8	4½ yr.	Tetralogy of Fallot	Cyanosis at 7 days of age; frequent attacks of dyspnea and unconsciousness	Aorta and pulmonary artery filled on 1st film (1 to 2 sec.)	Potts-Smith-Gibson	Tetralogy of Fallot; pulmonary stenosis; dextroposition of aorta; interventricular septal defect; hypertrophy of right ventricle
9	10 yr.	Tetralogy of Fallot	Cyanosis since 4 mo.; Grade III systolic murmur; small heart with straight pulmonary area; pulmonary vascular pulsations diminished; ECG showed marked right auricular and right ventricular hypertrophy	Pulmonary infundibular stenosis; aorta and pulmonary artery seen at 1½ sec.; pulmonary artery of normal size	Brock valvulotomy	Pulmonary infundibular stenosis; bicuspid pulmonary valve; dextroposed aorta; high interventricular septal defect; marked right ventricular hypertrophy
10	3 wk.	Severe tetralogy with pulmonary atresia	Marked cyanosis since birth; Grade III systolic murmur; heart normal size; ECG showed right ventricular hypertrophy	Right antero-oblique: at 1 sec., right auricle, right ventricle, and aorta filled; aorta markedly dextroposed; pulmonary artery never fills	Potts-Smith-Gibson	Tetralogy of Fallot with marked dextroposition of aorta; stenosis of left pulmonary artery; patent ductus arteriosus
11	27 mo.	Tetralogy of Fallot	Cyanosis at 10 mo.; attacks of dyspnea and unconsciousness; Grade III systolic murmur; diminished vascular pulmonary markings; ECG showed right ventricular hypertrophy	Posteroanterior: 1 sec. right auricle, right ventricle, and aorta visualized; no pulmonary artery Posteroanterior: no visualization of dextroposed aorta; 1 yr. later, right antero-oblique view visualized simultaneously the aorta and pulmonary artery	Patient died suddenly on operating room table while anesthetic was administered before chest was opened; cardiac massage and epinephrine failed to revive him	Hypertrophy and dilatation of the right ventricle; interventricular septal defect; overriding aorta; pulmonary stenosis, valvular; infrapulmonary stenosis; subendocardial fibroelastosis; old area of encephalomalacia in the right supratemporal region
12	20 mo.	Tetralogy of Fallot	Cyanosis; systolic murmur over precordium, good 2d pulmonic sound; moderate enlargement of right ventricle, right auricle; diminished pulmonary vascular markings; ECG showed right ventricular hypertrophy	Simultaneous opacification of aorta and right auricle at 1 sec.; infundibular stenosis; very little dye in pulmonary arteries	Potts-Smith-Gibson; died 1 yr. later	Tetralogy of Fallot; infundibular stenosis; dextroposition of aorta; interventricular septal defect; hypertrophy of right ventricle

ished. However, the second sound may be normal in intensity, in all probability representing the second aortic sound of the dextroposed aorta. 4. On roentgenograms the heart is small, and it remains small, enlarging only slightly as time goes on. The left middle arch on the posteroanterior view may be concave or straight, depending upon the size of the pulmonary artery. The patient in Case 9 (Table 2) had a straight pulmonary area and pathologically showed a good-sized main pulmonary artery, although an infundibular stenosis was present. 5. On fluoroscopic examination pulmonary vascular pulsations are either not seen at all or are markedly

Fig. 2 (Case 12).—Tetralogy of Fallot. Posteroanterior view. Simultaneous filling of the aorta and the pulmonary artery at one second. Note infundibular stenosis.

diminished, and the lung fields appear clear. This is a most important and constant finding. 6. Electrocardiography shows right ventricular hypertrophy.

The angiocardiogram may add corroborative evidence to the clinical diagnosis. As exhibited by the cases in Table 2, the following features may be seen: 1. The most characteristic feature is that dye fills the aorta and the pulmonary artery simultaneously from the right ventricle. This is strong evidence for existence of an overriding aorta. In general, the denser the aorta in comparison to the pulmonary artery, the greater the degree of dextroposition of the aorta. Figure 2 (Case 12) shows simultaneous filling of the aorta and the pulmonary artery in a case of

tetralogy of Fallot. Figure 3 (Case 10) shows the aorta filling at one second in the posteroanterior and right antero-oblique views without filling of the pulmonary artery, which filled one-half second later. This was a case of tetralogy which showed marked dextroposition of the aorta and extreme pulmonary stenosis at autopsy. It is difficult to distinguish this angiocardiogram from that of a pseudotruncus arteriosus with pulmonary atresia and from a complete transposition of the great vessels with pulmonary stenosis. Cooley and co-workers [6] have previously pointed out this difficulty in distinguishing a tetralogy with severe pulmonary stenosis from a pseudotruncus angiocardiographically. 2. The infundibular or valvu-

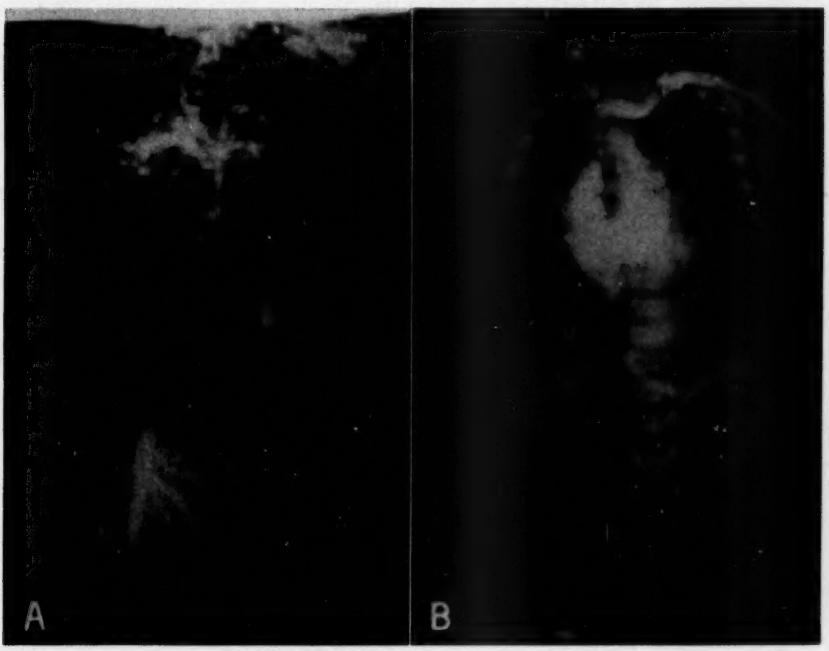

Fig. 3 (Case 10).—Tetralogy of Fallot. *A*, right antero-oblique view. Extreme dextroposition of the aorta. The aorta arch makes a wide sweep. *B*, posteroanterior view. At one second the pulmonary artery is not visualized because of extreme stenosis. The aorta is opacified and can be seen to arch to the right.

lar stenosis may be visualized on the angiocardiogram. This may be seen on either the posteroanterior or the right antero-oblique views. Figure 4 *A* (Case 9) shows definite infundibular stenosis with poststenotic dilatation at 1½ seconds. The defect is constant, still showing at 2½ seconds (Fig. 4 *B*). In order to diagnose pulmonary stenosis, the defect must remain constant in several succeeding films. If seen on only one film, a mistaken diagnosis of pulmonary stenosis may be made. Although we have visualized infundibular stenosis in several angiocardiograms in cases of

6. Cooley, R. N.; Bahnson, H. T., and Hanlon, C. R.: Angiocardiography in Congenital Heart Disease of Cyanotic Type with Pulmonary Stenosis or Atresia: Observations on the Tetralogy of Fallot and "Pseudo-Truncus Arteriosus," Radiology **52**:329-346, 1949.

tetralogy of Fallot, we feel that it is too inconstant a finding on which to depend for diagnosis. 3. The pulmonary artery may be small (Case 10), may be of normal caliber (Case 9), or may actually be dilated as in a valvular stenosis. The angiocardiogram is of value in giving the surgeon an idea of the size and position of the pulmonary arteries before operation. 4. If extreme pulmonary stenosis or atresia exists, the pulmonary artery may not be visualized until after the aorta (Fig. 3, Case 10), and then it may be impossible to differentiate this from a complete transposition of the great vessels. Case 11 is very interesting in that the angiocardiogram taken in the posteroanterior view failed to show a dextroposition of the aorta. We have seen at least two other patients with a clinical diagnosis of tetralogy of Fallot "proved" by catheterization and on the operating room table, who failed to show the dextroposition of the aorta angiocardiographically. This patient's arterial

Fig. 4 (Case 9).—Tetralogy of Fallot. *A*, posteroanterior view. Infundibular stenosis at 1½ seconds with poststenotic dilatation. Opacification of dextroposed aorta. *B*, posteroanterior view. Infundibular stenosis at 2½ seconds.

oxygen saturation at the age of 9 months was 93%. This normal arterial oxygen saturation and the failure of the angiocardiogram to reveal the dextroposition of the aorta threw great doubt on the diagnosis of tetralogy of Fallot. The subsequent development of cyanosis, low arterial oxygen saturation (68%), and another angiocardiogram taken one year later revealing a simultaneous opacification of the aorta and of the pulmonary artery established the diagnosis of tetralogy of Fallot. This autopsy proves beyond any doubt that patients with tetralogy of Fallot may exceptionally have no cyanosis, a normal arterial oxygen saturation, and may show no angiocardiographic evidences of dextroposition of the aorta.

3. Common Trunk (Pseudotruncus Arteriosus): Pathologically, two types of common trunk may be described: 1. In the true truncus communis the trunk arises from both right and left ventricles and gives off the right and left pulmonary arteries from the ascending aorta. In this condition the pulmonary arteries are large and there is a good pulmonary blood flow. 2. In the pseudotruncus there is no main pulmonary artery, there being an atresia of the pulmonary valve. The

TABLE 3.—*Common Trunk*

Case	Age at Death, Mo.	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Diagnosis	Surgery	Autopsy Findings
13	9	Common trunk	Cyanosis since birth; Grade IV systolic murmur, loud 2d pulmonic sound; enlarged heart, narrow base, apex markedly elevated; diminished pulmonary vascular pulsations; ECG showed combined ventricular hypertrophy	Posteroanterior injection right arm: tremendous aorta coming off right ventricle at ½ sec.; small pulmonary artery at 1 sec. Left antero-oblique injection left arm: persistent left superior vena cava enters left auricle, also going into right auricle; vessel filling by reflex from right superior vena cava; large aorta from right ventricle at 1 sec.; pulmonary artery small, seen at 3 sec.	Blalock-Taussig	Pseudotruncus arteriosus; atresia of main pulmonary artery; patent ductus arteriosus; persistent left superior vena cava entering left auricle and anastomosing with right auricle; anomalous inferior vena cava entering superior vena cava (right)
14	28	Common trunk; levocardia; right aortic arch	Cyanosis; situs inversus with heart on left; enlarged heart with large left ventricle; barium swallow; right aortic arch open up; diminished vascular pulmonary pulsations; ECG showed no axis shift	Posteroanterior: tremendous aorta with right aortic arch at 1½ sec.; small pulmonary artery Right antero-oblique: large aorta from right ventricle at 1½ sec.; small pulmonary artery	Exploratory	Single ventricle; pseudotruncus with right aortic arch; pulmonary atresia; left persistent superior vena cava with pulmonary vein going into it; right pulmonary vein emptying into ductus venosus; situs inversus with levocardia; interauricular defect

TABLE 4.—*Tricuspid Atresia*

Case	Age at Death, Yr.	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Surgery	Autopsy Findings
15	½	Tricuspid atresia	Cyanosis since birth; systolic murmur over precordium; heart slightly enlarged; concavity in pulmonary area; small right ventricle, enlarged left ventricle; polycythemia; ECG showed left ventricular hypertrophy and right auricular hypertrophy	Shunt from right auricle to left auricle; aorta seen at 1 sec.; small pulmonary artery at 1½ sec.; rudimentary right ventricle	0	Right auricle markedly dilated and hypertrophied; large interauricular septal defect; tricuspid valve extremely stenotic, but probe passed; hypoplastic right ventricle; atresia of pulmonary valve; patent ductus arteriosus
16	1	Tricuspid atresia	Cyanosis since birth; small heart with concavity in pulmonary area; systolic murmur over precordium; diminished pulmonary vascular pulsations; small right ventricle, enlarged left ventricle; ECG showed left ventricular hypertrophy	Dye in right auricle, left auricle, on Film 2 (about 1-2 sec.)	Potts-Smith at 7 mo.; heart enlarged rapidly following surgery; died at 1 yr.	Absence of tricuspid valve; hypoplasia of right ventricle; large interauricular septal defect; patent ductus arteriosus; healed anastomosis between descending aorta and left pulmonary artery; hypoplasia of pulmonary artery; marked dilatation of right auricle and left ventricle; bronchopneumonia

pulmonary arteries are, therefore, supplied with blood via a patent ductus, or the lungs are supplied by bronchial arteries. In this condition there is a diminished pulmonary blood flow. The two cases presented in this series (Table 3) are cases of pseudotruncus. Each of them had many associated anomalies.

In Case 13 a white girl baby, 8½ months of age, showed the following clinical features: 1. Dyspnea and cyanosis, present since birth, were becoming progressively more severe. 2. A Grade IV systolic murmur was present over entire precordium with an accentuated second pulmonic cound. 3. Roentgenograms in the posteroanterior view revealed a markedly enlarged heart with a narrow base and

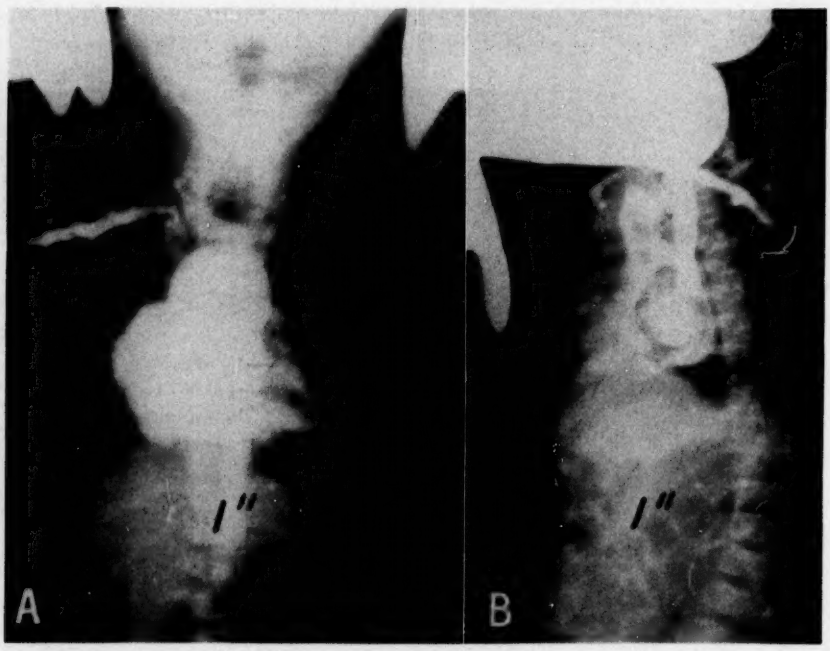

Fig. 5 (Case 13).—Pseudotruncus arteriosus. *A*, posteroanterior view. A huge common truncus and a small pulmonary artery. *B*, posteroanterior view. Persistent left superior vena cava emptying into the left auricle and the right auricle.

markedly elevated apex. There was a concavity in the pulmonary region and enlargement of the right auricle. The left antero-oblique view revealed marked enlargement of both the right auricle and the right ventricle. Fluoroscopy revealed diminished pulmonary vascular pulsations. 4. Electrocardiograms showed evidence of both right and left ventricular hypertrophy. On the basis of these findings a clinical diagnosis of pseudotruncus was made. Angiocardiography was performed in the posteroanterior and left antero-oblique views. In both views a large trunk was noted filling from the right ventricle at one-half second, and a small pulmonary artery at one second (Fig. 5 *A*, Case 13). In addition to this, the injection into the left arm for the left antero-oblique view revealed a persistent left superior vena cava emptying into the right auricle via the coronary sinus (Fig. 5 *B*). A com-

municating branch with the right superior vena cava is also noted and another aberrant vessel below it, which, on autopsy, was identified as an anomalous inferior vena cava coursing up the posterior mediastinum and emptying into the right superior vena cava just above its entrance into the right auricle. The postero-anterior view does not show these venous anomalies since the injection was made into the right arm, the dye thus not entering the left superior vena cava. This demonstrates the importance of getting more than one view and injecting into both arms in order to make a more complete anatomical diagnosis. The patient had a Blalock-Taussig operation, but died postoperatively. The autopsy revealed the following: (*a*) a markedly enlarged heart, (*b*) atresia of the pulmonary valve, (*c*) a large truncus aorticus coming off both the right and the left venticle, (*d*) a high interventricular defect, (*e*) a patent ductus arteriosus, (*f*) a persistent left superior vena cava entering the left auricle, (*g*) the anomalous course of the inferior vena cava emptying into the right superior vena cava.

Case 14 (a 13-month-old white girl) presented the following clinical features: 1. Cyanosis was present since birth, increasing in severity. 2. The red blood cell count was 7,520,000; the hemoglobin value, 18 gm. per 100 cc. 3. The roentgenogram of the chest revealed the heart on the left side. However, roentgenograms of the abdomen as well as a gastrointestinal study revealed presence of situs inversus. Therefore, she had a levocardia with situs inversus. The heart was moderately enlarged, the cardiothoracic ratio being 60%. On posteroanterior view, the pulmonary segment was convex. On right antero-oblique view, the conus region was also convex. Left antero-oblique view revealed enlargement of the left ventricle, the latter structure not clearing the spine. 4. Barium swallow revealed presence of a right aortic arch. 5. On fluoroscopic examination the pulmonary vascular pulsations were diminished. 6. The electrocardiogram showed no axis shift. A clinical diagnosis of levocardia, a pseudotruncus and right aortic arch was made. Angiocardiography was performed in the posteroanterior and right antero-oblique views, both injections being into the right arm. In the posteroanterior view, dye filled what appeared to be a single ventricle. A very large aorta filled at 1½ seconds, and the right aortic arch was visualized. A small pulmonary artery was also visualized at 1½ seconds. The chambers of the heart were arranged in normal order for a left-sided heart. The right antero-oblique view showed the same features. The small pulmonary artery appeared to have no connection with the ventricle, thus probably filling through a ductus or through bronchial arteries. The angiocardiograms then seemed to corroborate the clinical impression of situs inversus with levocardia, common trunk (pseudotruncus), and right aortic arch. Cardiac catheterization was then performed and revealed the following findings: 1. Oxygen content in the superior vena cava was 12.57 vol. %, in the inferior vena cava 9.91 vol. %, in the upper right auricle 12.50 vol. %, lower right auricle 11.73 vol. %, right ventricle 11.30 vol. %, and in the aorta 11.63 vol. %. The pressure in the right ventricle was 80/5, and in the aorta 80/60. The presence of a higher oxygen content in the superior vena cava than in the aorta was interpreted to mean that the former was receiving oxygenated blood. Therefore, a diagnosis of one or more pulmonary veins entering the superior vena cava was made. Because the systolic pressures in the ventricle and aorta were identical, it was felt that a single ventricle was probably present. Because the aorta was easily entered, and no

pulmonary artery was entered, a common trunk was diagnosed. Thus, cardiac catheterization added to the diagnosis by establishing the presence of an aberrant pulmonary venous drainage into the superior vena cava. Exploratory surgery was done, but the patient died on the table. Autopsy revealed the following cardiac pathology: (*a*) heart moderately enlarged, (*b*) a single ventricle present plus a small rudimentary chamber, (*c*) left persistent superior vena cava with one of the left pulmonary veins emptying into it, (*d*) interauricular defect, (*e*) right aortic

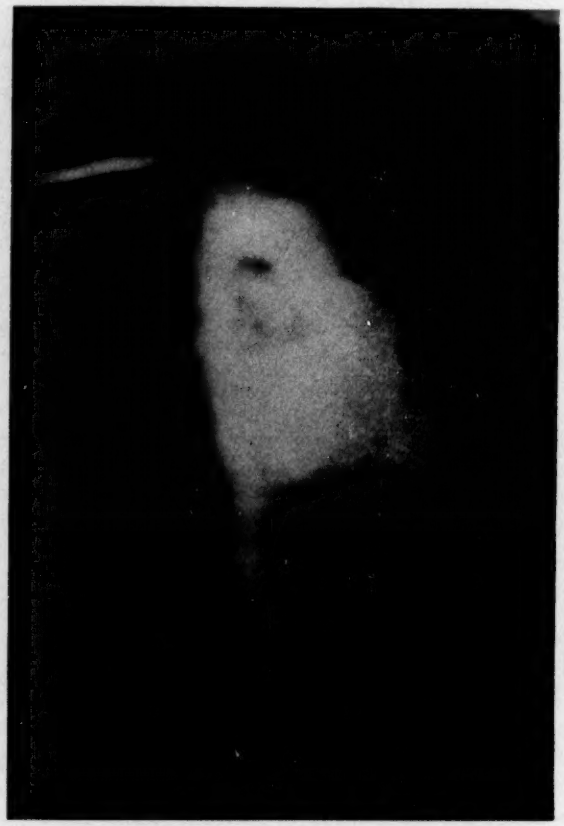

Fig. 6 (Case 14).—Pseudotruncus arteriosus with a huge aorta which arches to the right.

arch, (*f*) atresia of main pulmonary artery. This case demonstrates very well that by correlation of the clinical examination, the angiocardiogram, and cardiac catheterization, an almost complete diagnosis was made of the multiple cardiac anomalies. These findings correlated well with the autopsy findings. It must again be pointed out that from an angiocardiographic standpoint alone, differentiation between pseudotruncus and extreme tetralogy of Fallot with severe pulmonary stenosis or atresia (Case 10, Table 2) is difficult. However, the large size of the aorta in the pseudotruncus helps differentiate between the two. In Case 14 the small pulmonary

TABLE 5.—*Ebstein's Anomaly*

Case	Age at Death	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Surgery	Autopsy Findings
17	3 wk.	Severe tetralogy with pulmonary atresia, or aortic and mitral atresia	Severe cyanosis at birth; marked cardiac enlargement at birth; Grade III systolic murmur at left sternal border; enlargement of right auricle and left ventricle; marked decreased pulmonary vascular markings; right auricular and left ventricular hypertrophy on ECG; intraventricular conduction defect	Posteroanterior: superior vena cava and inferior vena cava empty into what appears to be left auricle; at ½ sec., left auricle dense, right auricle extremely large, light; pulmonary artery seen at 1 sec., aorta dense at ½ sec.; late reopacification of tremendous right auricle Left antero-oblique: tremendous light right auricle and dense left auricle at ½ sec.; aorta and small pulmonary artery at 1 sec.; no definite right ventricle seen; late reopacification of right auricle	Exploratory	Heart markedly enlarged; tremendous right auricle and right auricular appendage; tricuspid ring at normal site, but valve displaced downwards into right ventricle; right ventricular chamber tiny; large interauricular septal defect; patent foramen ovale; patent ductus arteriosus
18	16 mo.	Tricuspid atresia	Cyanosis since birth; loud systolic murmur heard at left 2d interspace; enlarged heart with pulmonary concavity; right ventricle small, left ventricle large; ECG showed left ventricular hypertrophy	Posteroanterior: right auricle large, left auricle, with appendage at ½ sec.; aorta seen at 1 sec. small pulmonary artery at 1½ sec. Left antero-oblique: right auricle dense, left auricle seen at 1 sec.; aorta and pulmonary artery at 2½ sec.; right ventricle small	Nov. 26, 1951; Potts-Smith; died Nov. 28, 1951	Heart moderately enlarged; right auricle tremendously dilated; right auricular appendage dilated; tricuspid ring in normal position; downward displacement of tricuspid valve; pulmonary artery hypoplastic; large interauricular septal defect; ductus botalli closed

artery was visualized simultaneously with the aorta, as occurs in a tetralogy. However, the tremendous aorta gives definite support to the diagnosis of pseudotruncus (Case 14, Fig. 6).

4. Tricuspid Atresia (Table 4): The pathological anatomy in this malformation consists of atresia of the tricuspid valve, rudimentary right ventricle, hypoplasia of the pulmonary artery, and an interauricular septal defect.

The clinical features of this malformation consist of the following: 1. Cyanosis is present at birth, becoming progressively worse with age. 2. Auscultation reveals a systolic murmur over the left parasternal area. The second pulmonic sound is diministed. 3. Roentgenograms reveal a small heart with a concavity in the pulmonary area on the posteroanterior view. The left antero-oblique view reveals a small right ventricle ("chopped-off" anterior border) and enlargement of the left ventricle. 4. Fluoroscopy reveals diminished pulmonary vascular pulsations. 5. The electrocardiogram shows left axis deviation and left ventricular hypertrophy. In this series the two cases presented (Table 4) were quite typical clinically. However, in some instances, the picture may not be clear-cut, and further laboratory work-up is necessary.

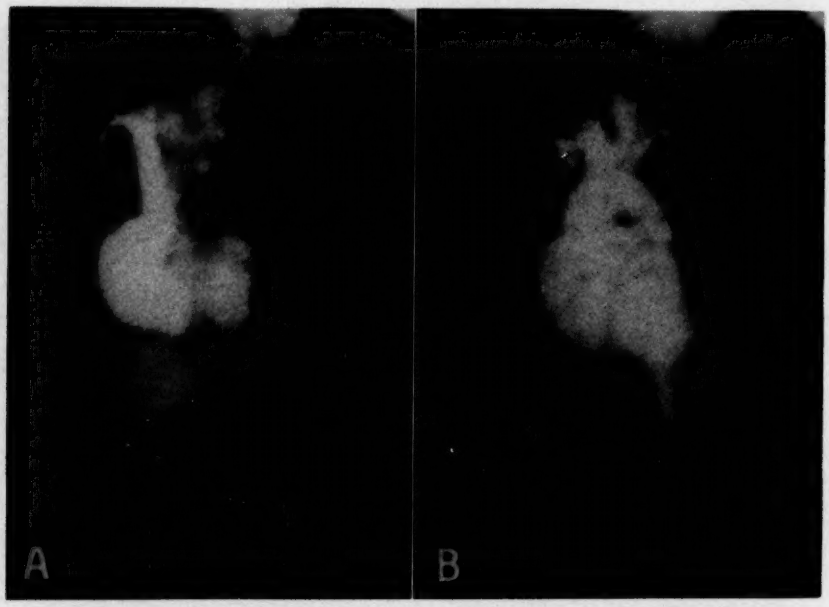

Fig. 7 (Case 15).—Tricuspid atresia. *A*, left antero-oblique view. At one second dye is seen entering the left auricle from the right auricle. *B*, left antero-oblique view. At three seconds a large aorta, a small pulmonary artery, and a hypoplastic right ventricle are shown.

Angiocardiography shows the following features: 1. Dye is seen going directly from the right auricle into the left auricle (Fig. 7 *A*, Case 15). 2. The aorta is well filled by 1 to 1½ seconds, coming off the left ventricle. 3. The pulmonary artery is small and usually is visualized one-half to one second after the aorta. 4. The hypo-

plastic right ventricle may be seen in later films, filling from the left ventricle through an interventricular defect (Fig. 7 *B*). 5. Dye is usually gone from the heart by five to six seconds in infants. The shunt from the right auricle to the left auricle is one-way with very little reversal of the shunt. Therefore, no reopacification of the right auricle occurs.

5. Ebstein's Anomaly: This unusual cardiac malformation was first described by Ebstein in 1866.[7] Since then 27 cases have been reported in the world literature. The most recent addition to the literature was made by Engle, Payne, Bruins, and Taussig [8] in 1950, with the reporting of three proved cases and a complete review of the literature. Included in their report were the angiocardiographic and cardiac catheterization findings in their cases. We believe that the patients in the two cases reported here are the youngest in cases that have been reported with clinical and laboratory studies.

The pathology of this anomaly consists essentially of a congenital downward displacement of the tricuspid valve into the right ventricle so that the leaflets, instead of arising normally from the annulus fibrosus, arise below this from the walls of the right ventricle. The valve leaflets are usually deformed. In some instances, the anterior leaflets may arise normally from the ring. Thus, the portion of the right ventricle above the valve becomes functionally incorporated into the right auricle and may be referred to as the "auricularized right ventricle." The functioning right ventricle is markedly diminished in volume, usually consisting of only the apex of the right ventricle and the conus region. An associated patent foramen ovale or interauricular defect may be present, or the interauricular septum may be intact. The pulmonary arteries may be hypoplastic. The pathology of this malformation may vary tremendously in degree from very mild, in which case the patient may live a fairly normal lifetime with few, if any, clinical symptoms, to very severe, in which case the individual may die in very early infancy (Case 17, Table 5).

The pathologic physiology depends upon the severity of the malformation. In the mild case the circulation through the heart and to the lungs may be perfectly normal. However, in severe cases, such as those presented in Table 5, the course of the circulation is seriously altered. If there is an interauricular communication present, a right-to-left shunt will occur. The unoxygenated blood from the right auricle thus goes to the left auricle, then into the left ventricle and out into the aorta, giving rise to cyanosis. The cyanosis is either subclinical or clinical, depending upon the volume of the right-to-left shunt. The blood entering the small right ventricle travels to the lungs via the hypoplastic pulmonary artery, then back into the left auricle. The right auricle becomes progressively more dilated and hypertrophied and accounts for a large part of the rapid cardiac enlargement. Cyanosis and dyspnea become progressively worse, and the young patient dies of right heart failure. It will be noted that the course of the circulation in Ebstein's anomaly may be quite similar to that in tricuspid atresia, except that in the former some blood does enter the right ventricle from the right auricle.

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7. Ebstein, W.: Über einen sehr seltenen Fall von Insufficienz der Valvula tricuspidalis, bedingt durch eine angeborene hochgradige Missbildung derselben, Arch. Anat., Physiol. u. Wissensch. Med., 1866, pp. 238-254.

8. Engle, M. A.; Payne, T. P. B.; Bruins, C., and Taussig, H. B.: Ebstein's Anomaly of the Tricuspid Valve: Report of 3 Cases and Analysis of Clinical Syndrome, Circulation **1**:1246-1260, 1950.

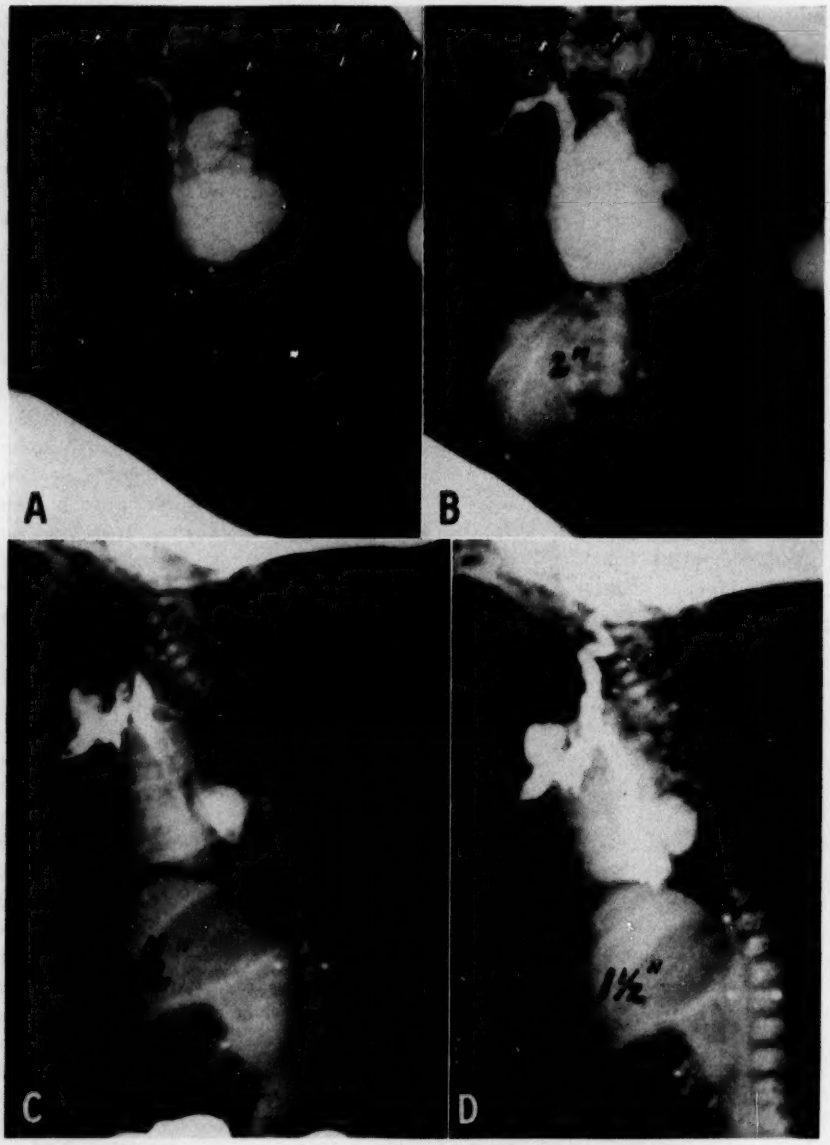

Fig. 8 (Case 17).—Ebstein's anomaly. *A*, posteroanterior view. At one-half second the large right auricle, left auricle with a large appendage, large aorta, and small pulmonary artery are visualized. *B*, posteroanterior view. At two seconds all chambers are opacified. *C*, left antero-oblique view. At one-half second the superior vena cava appears to enter the left auricle, which is more opacified than the right auricle. *D*, left antero-oblique view. At 1½ seconds the right auricle, the left auricle, and the aorta are visualized.

In Case 17, a newborn Negro baby girl was noted to be intensely cyanotic at birth. Auscultation revealed a gallop rhythm, a Grade III systolic murmur at the left sternal border, and a questionable diastolic murmur. The red blood cell count was 4,540,000, and the hemoglobin concentration was 105%. Roentgenograms on the second day of life revealed marked generalized cardiac enlargement, the cardiothoracic ratio being over 75%. The right auricle was markedly enlarged on the posteroanterior and left antero-oblique projections. It was difficult to evaluate the size of the right ventricle. On the left antero-oblique projection the left ventricle bulged markedly posteriorly and did not clear the spine. Fluoroscopy on the third day of life showed the same configuration as the roentgenograms. Pulmonary vascular pulsations appeared diminished. The electrocardiogram revealed marked hypertrophy of the right auricle and the left ventricle and an intraventricular conduction defect. The clinical impression was, first, severe tetralogy of Fallot with pulmonary atresia or extreme stenosis, or, second, because of the tremendous enlargement of the heart at birth, aortic atresia.

Angiocardiography, performed on the 6th and 10th days of life, produced very controversial results. Two posteroanterior views, one with the injection into the saphenous vein and the other into the right brachial vein, showed a very dense left auricle and a tremendous but pale right auricle at one-half second (Fig. 8 *A*, Case 17). In fact, the dye appeared in both to be emptying directly into the left auricle from the inferior vena cava and the superior vena cava, respectively, and then entering the right auricle through an interauricular septal defect (Fig. 8 *B*, Case 17). A tremendous right auricular appendage and a large left auricular appendage were also seen. The aorta opacified at one-half second, but the small pulmonary artery did not opacify until one second. The right auricle reopacified in later films. The left antero-oblique angiocardiogram revealed similar findings (Fig. 8 *C* and *D*, Case 17). The impression gained from the angiocardiogram was that this might be a case of both venae cavae entering the left auricle only, with an interauricular septal defect. Therefore, an exploratory operation was performed. Nothing was done, however, when it was seen that the superior and inferior venae cavae emptied into a tremendously dilated right auricle. The patient died the evening of operation.

Autopsy revealed the following: 1. The heart was markedly enlarged. 2. The right auricle was markedly enlarged. 3. The superior and inferior venae cavae were dilated. 4. The tricuspid ring was normally situated, but no valve arose from it. Instead, the tricuspid valve arose from the walls of the lowermost portion of the right ventricle. 5. The right ventricular cavity was tiny and contained only a few cubic centimeters of blood. 6. There was a large interauricular septal defect. 7. A patent foramen ovale was found. 8. There was a patent ductus arteriosus. 9. The left ventricle was hypertrophied.

In Case 18 a white girl, who was studied at the ages of 10 months and of 16 months, presented the following clinical features: 1. Cyanosis was present since birth, but the patient did fairly well until one year of age, when cyanosis and exertional dyspnea became more severe. 2. There was clubbing of the fingers and toes. 3. A loud systolic murmur was found which was heard best in the left parasternal area and a diastolic murmur, heard best in the left second interspace. The second pulmonic sound was diminished. 4. The red blood cell count was 6,530,000; the hemoglobin value, 17.28 gm. per 100 cc. Roentgenograms revealed a progressively

enlarging heart, from a cardiothoracic ratio of 60% at 10 months to 67% at 16 months. There was a concavity in the pulmonary area. In the left antero-oblique view the right auricle appeared enlarged, the right ventricle small, and the left ventricle enlarged. Fluoroscopy revealed diminished pulmonary vascular pulsations. 5. The electrocardiogram revealed a semivertical heart with left ventricular hypertrophy. There was no intraventricular conduction defect. A clinical diagnosis of tricuspid atresia was made, and the child was then subjected to physiologic studies.

Angiocardiography was performed at 10 months in both posteroanterior and left antero-oblique projections. The posteroanterior view showed the right auricle and the left auricle with an enlarged appendage at one-half second (Fig. 9 *A*, Case

Fig. 9 (Case 18).—Ebstein's anomaly. *A*, posteroanterior view. At one second dye enters the left auricle from the right auricle. Note the left auricular appendage. *B*, left antero-oblique view. At one second, large left auricle and right auricle.

18). At 1 second the left ventricle and aorta were seen, and by 1½ seconds, a small pulmonary artery was visualized. In the left antero-oblique view a large right auricle and a large dense left auricle with appendage were seen at one second (Fig. 9 *B*, Case 18). Due to a slow injection, the aorta and left ventricle were not visualized until 2½ seconds, and the small pulmonary artery was seen at 3 seconds. At four seconds, the dye could be seen in a small right ventricle going into the pulmonary artery. The right auricle reopacified and appeared very large. The angiocardiographic interpretation was consistent with a diagnosis of tricuspid atresia.

Because of the diastolic murmur which was atypical for a tricuspid atresia, cardiac catheterization was performed. The right ventricle could not be entered from the auricle. The catheter passed through an interauricular septal defect into the left auricle and then into the left ventricle. The oxygen content in the superior vena cava was 6.14 vol. %, in the left auricle, 8.76 vol. %, in the left ventricle 9.24

vol. %, in the femoral artery, 9.18 vol. %, in the inferior vena cava, 6.16 vol. %, and in the right auricle 6.49 vol. %. These findings were considered consistent with a tricuspid atresia or stenosis.

With the preoperative diagnosis of tricuspid atresia felt to be firmly established, a Potts-Smith operation was performed. The child had a stormy postoperative course and died on the 12th postoperative day.

Autopsy revealed the following features: 1. The heart was moderately enlarged, the apex being formed entirely by the left ventricle. 2. The superior and inferior venae cavae were dilated. 3. The right atrium and the right auricular appendage were markedly dilated and hypertrophied. 4. The ring of the tricuspid valve was in its normal position and of normal (5.0 cm.) diameter. 5. The tricuspid valve was displaced downward into the right ventricle, 2.5 cm. below the ring, and was only 0.5 cm. in diameter. 6. The right ventricle was a tiny pocket measuring only a few millimeters in cross section. 7. A large interauricular septal defect measuring 3.5 cm. by 4.5 cm. was present. 8. The pulmonary artery was hypoplastic, the pulmonary valve measuring only 1.75 cm. in diameter. 9. The ductus botalli was obliterated.

These two cases present several very interesting clinical and laboratory findings. Case 17 indicates that Ebstein's anomaly, in its severest form, must be added to the few malformations that can give a markedly enlarged heart at birth. A cyanotic infant with an enlarged heart, an electrocardiogram showing left ventricular hypertrophy, and possibly an intraventricular conduction defect should suggest this diagnosis in a newborn or young infant. Angiocardiography in this case was actually misleading. The superior vena cava and the inferior vena cava appeared to be entering the left auricle. The great density of the left auricle compared to the light right auricle supported this interpretation. Correlation of these findings with the electrocardiographic evidence of left ventricular hypertrophy lent considerable evidence to the diagnosis of both venae cavae entering the left auricle, a rare anomaly. This angiocardiographic finding is still difficult to explain. The most reasonable explanation is that a "current" of dye passed directly from the superior vena cava through the interauricular septal defect, into the left auricle, while the rest of the dye was being diluted by the tremendous volume of blood in the right auricle. In spite of the error in interpretation, however, an angiocardiographic pattern has been shown which, correlated with these clinical and pathologic findings, may be of value in diagnosing future cases of this type of Ebstein's anomaly. Case 18 brings up the problem of differentiating a moderately severe Ebstein's anomaly from tricuspid atresia. The similarity of the abnormal circulation in these two conditions has already been pointed out. Also it will be noted that the clinical, angiocardiographic, and cardiac catheterization findings in this patient were very similar to those found in tricuspid atresia. Possibly the crucial differentiating point in this case was the heart size. It is known that in tricuspid atresia the heart size is normal or slightly enlarged. However, in this case the heart became progressively enlarged. This finding should suggest Ebstein's anomaly in a case which otherwise strongly resembles tricuspid atresia. In this case the angiocardiographic findings were indistinguishable from those of tricuspid atresia, which demonstrates a limitation of angiocardiography. Likewise, the two conditions were not differentiated by cardiac catheterization in this case.

TABLE 6.—*Pentalogy*

Case	Age at Death, Mo.	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Surgery	Autopsy Findings
19	4	Possible septal defect	No cyanosis noted; red blood cell count 3,200,000; Grade III systolic murmur; 2d pulmonic sound louder than 2d aortic sound; enlarged right auricle and right ventricle, elevation of apex; ECG showed right ventricular hypertrophy with left heart strain	Left antero-oblique: left auricle seen at 1 sec.; dense aorta, small pulmonary artery at 1 sec.; small amount of dye in lungs; dye remained in heart until 9 sec. with continuous reopacification of right auricle, right ventricle, and pulmonary artery	0	Pulmonary stenosis; dextraposed aorta; high interventricular septal defect; interauricular septal defect; patent foramen ovale; ductus botalli closed; marked right ventricular hypertrophy (wall 5 mm.); left ventricular hypertrophy (wall 7 mm.)
20	2	Tricuspid atresia Types I and II	Cyanosis since birth; Grade IV systolic murmur; progressive cardiac enlargement; small right ventricle, large right auricle, large left ventricle; ECG showed left ventricular and right auricular hypertrophy	Large right auricle, left auricle at ½ sec.; aorta at 1 sec.; small pulmonary artery at 1½ sec.; continuous late reopacification of right auricle	0	Marked enlargement; pulmonary atresia; high interventricular septal defect; dextraposed aorta; interauricular septal defect; right ventricular hypertrophy (wall 5 mm. thick); patent ductus arteriosus; left ventricular hypertrophy (wall 7 mm. thick)

6. Tetralogy of Fallot with an Interauricular Communication (Pentalogy): Gasul, Richmond, and Krakower [9] described the first proved case of this malformation which was studied clinically. This anomaly is identical pathologically with the tetralogy of Fallot with the added feature of an interauricular communication, either a septal defect or a functionally patent foramen ovale. However, this added defect alters the clinical course appreciably. The course of the circulation has an additional route through the heart, i. e., some of the blood is shunted from the right auricle through the interauricular defect into the left auricle, left ventricle, and aorta. This places an added strain on the left ventricle, causing it to hypertrophy, thus accounting for the progressive cardiac enlargement.

The clinical features of this condition are similar to those of tetralogy of Fallot with two notable exceptions: 1. The heart undergoes progressive enlargement. 2. There is moderate to marked hypertrophy of the left ventricle, which is seen in the left antero-oblique roentgenograms. In addition, the electrocardiogram may show combined right and left ventricular hypertrophy, as in Case 19 (Table 6).

Case 19 (Table 6) presents several interesting features. Cyanosis was never noted in this baby, although she remained dyspneic and had to stay in oxygen. Although she weighed 5 lb. 15 oz. (2,700 gm.) at birth, she weighed only 4 lb. 7 oz. (2,010 gm.) when readmitted for cardiac study. Therefore, this patient was considered in the noncyanotic category for cardiac malformation, and a septal defect was tentatively diagnosed. However, angiocardiography was done in the left antero-oblique projection and demonstrated a dextroposed aorta, pulmonary stenosis, and an interauricular septal defect. These findings correlated with the autopsy findings (Table 6).

Case 20 (Table 6) presented another problem in differential diagnosis. This patient was cyanotic at birth, and auscultation at 2 weeks of age revealed a loud systolic murmur over the entire precordium. Serial roentgenograms at the age of 2, 4, and 6 weeks of age revealed the heart to be rapidly enlarging, from a cardiothoracic ratio of 62% up to one of 75%. The apex was elevated, the right auricle enlarged, the pulmonary area straight. At 2 weeks the left antero-oblique view showed a small right ventricle and enlargement of the left ventricle. The pulmonary vascular pulsations were diminished. Since the electrocardiogram showed marked left ventricular hypertrophy, a clinical diagnosis of tricuspid atresia was made. However, by 6 weeks of age the heart had enlarged tremendously, roentgenograms of the right ventricle showed enlargement in the left antero-oblique view, and the electrocardiogram still showed left ventricular hypertrophy with right auricular hypertrophy. It was evident at this time that this was not the usual case of tricuspid atresia. Angiocardiography in the left antero-oblique position was performed and showed the following: 1. There was a very large right auricle with marked enlargement of the right auricular appendage. 2. At one-half second, dye was also in the left auricle, indicating an interauricular right-to-left shunt (Fig. 10 *A*, Case 20). However, in this particular view, it could not be determined whether a right ventricle was present or not, because the right auricle was greatly enlarged and superimposed upon the right ventricular region. 3. The aorta was first seen at 1 second,

9. Gasul, B. M.; Richmond, J. B., and Krakower, C. A.: A Case of Tetralogy of Fallot with a Patent Foramen Ovale (Pentalogy) Showing a Marked Left Ventricular Hypertrophy and Left Axis Deviation, J. Pediat. **35**:413-421, 1949.

but was dense by 1½ seconds. 4. A small pulmonary artery was first seen at two seconds. 5. The right auricle continued to reopacify (Fig. 10 *B*, Case 20). 6. Dye disappeared from the heart by seven seconds. These findings were consistent with the diagnosis of tricuspid tresia, so angiocardiography was of no value in solving the problem. Autopsy revealed the following: (*a*) markedly enlarged heart, weighing 75 gm., (*b*) hypertrophy of the right ventricle (wall 5 mm. thick) and of the left ventricle (wall 7 mm. thick), (*c*) dextroposition of the aorta, (*d*) pulmonary atresia, (*e*) interventricular septal defect 7 mm. in diameter, (*f*) interauricular

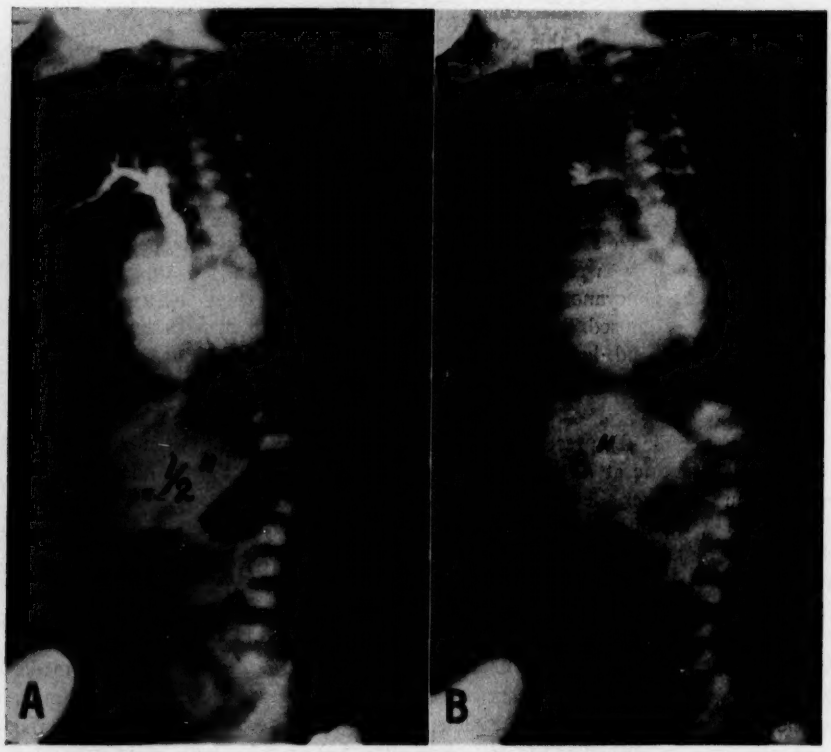

Fig. 10 (Case 20).—Pentalogy. *A*, left antero-oblique view. At one-half second dye enters the left auricle from the right auricle. *B*, left antero-oblique view. At six seconds the right auricle is reopacified.

defect 1 cm. in diameter, and (*g*) patent ductus arteriosus. These findings constitute a pentalogy.

The clinical, angiocardiographic, and pathologic findings can be well correlated in the above, in retrospect. The pulmonary atresia and the interauricular septal defect led to a large shunt of blood from the right auricle into the left auricle and ventricle, causing the marked progressive hypertrophy of the left ventricle as well as of the right ventricle, and accounting for the rapid enlargement of the heart. This also accounts for the finding of left ventricular hypertrophy on the electrocardiogram. On the angiocardiogram (left antero-oblique) this shunt led to an

early visualization of the left auricle and left ventricle, similar to a tricuspid atresia. Because of the pulmonary atresia, the pulmonary artery had to fill through a ductus and, therefore, was not visualized until one-half second after the aorta and was very small when visualized. This is also consistent with the angiocardiographic findings in tricuspid atresia. In this left antero-oblique view, the filling of the right ventricle was masked by the large superimposed right auricle, so that the size or even the presence of a functioning right ventricle could not be accurately determined. Thus, it is seen that this angiocardiogram strongly resembled that of a tricuspid atresia. However, one important difference is evident in retrospect. In Figure 10 *B* it is seen that the right auricle in Case 20 is continuing to reopacify. The pressure in the right auricle, although somewhat elevated, is not sufficiently elevated to present some left-to-right shunt, leading to a bidirectional shunt, and therefore reopacification of the right auricle with dye is seen in the later films. These findings have not been noticed in any of the angiocardiograms of tricuspid atresia that have been reviewed. In the latter, the shunt is strictly right to left, because of the very high pressure in the right auricle. Therefore, there is no later reopacification of the right auricle. In fact, the heart is usually emptied of dye by five to six seconds. It is felt that this may be an important angiocardiographic sign to differentiate a pentalogy from tricuspid atresia.

Clinically, a pentalogy must be differentiated from tetralogy of Fallot, tricuspid atresia, Ebstein's deformity, and isolated pulmonary stenosis with an interauricular communication (to be discussed next). The progressive enlargement of the heart and the electrocardiographic finding of left ventricular hypertrophy help differentiate this from tetralogy of Fallot. The progressive enlargement of the heart, with perhaps some electrocardiographic evidence of right auricular hypertrophy as well as left (as in Case 19), seems to differentiate this condition from tricuspid atresia. Evidence of right ventricular hypertrophy as well as absence of an intraventricular conduction defect will help differentiate it from Ebstein's anomaly.

7. Pulmonary Valvular Stenosis with Interauricular Communication (Table 7): The clinical syndrome of pulmonary stenosis with a patent foramen ovale or interauricular septal defect has recently been described in publications by Engle and Taussig [10] and Selzer and co-workers.[11] The pathology of this malformation consists of a pulmonary valvular stenosis with an intact ventricular septum and an interauricular communication, either a functionally patent foramen ovale or an interauricular septal defect. The latter defect is the only additional feature which distinguishes this condition pathologically from isolated pulmonary stenosis.

The severity of the clinical syndrome depends upon the degree of pulmonary stenosis and the size of the interauricular communication. The usual clinical features are as follows: 1. Cyanosis is usually absent at birth but begins to show during the first year of life or even much later. In severe cases cyanosis is present at birth. The cyanosis is due to the shunt of unoxygenated blood from the right to the left auricle as the pressure in the auricle rises. 2. Auscultation reveals a loud systolic murmur heard best over the pulmonary area. The second pulmonic sound

10. Engle, M. A., and Taussig, H. B.: Valvular Pulmonic Stenosis with Intact Ventricular Septum and Patent Foramen Ovale: Report of Illustrative Cases and Analysis of Clinical Syndrome, Circulation **2**:481-493, 1950.

11. Selzer, A.; Carnes, W. H.; Noble, C. A., Jr.; Higgins, W. H., Jr., and Holmes, R. A.: The Syndrome of Pulmonary Stenosis with Patent Foramen Ovale, Am. J. Med. **6**:3-23, 1949.

is diminished. There may be a systolic thrill palpable over this area. 3. Roentgenograms may reveal a normal-sized heart at birth which becomes progressively enlarged during the first or following years. In severe cases the heart may be moderately to markedly enlarged at birth. The configuration of the heart on the posteroanterior view shows straightening or bulging of the pulmonary area and enlargement of the right auricular region to the right. In the left antero-oblique view, the right auricle and ventricle are both enlarged, and there is some enlargement of the left ventricle. In the right antero-oblique view, there is straightening of the pulmonary conus. 4. Fluoroscopy reveals diminished or normal pulmonary vascular pulsations. 5. The electrocardiogram usually shows marked right auricular and right ventricular hypertrophy. However, in severe cases, such as Case 21 (Table 7), there is a left ventricular preponderance shortly after birth. As the condition progresses, however, the right ventricular hypertrophy predominates, but some evidence of the left ventricular hypertrophy may remain.

The usual angiocardiographic features are as follows: 1. There is a shunt of dye from the right auricle into the left auricle at one-half second to one second. 2. Dye progresses normally into the right ventricle, then into the pulmonary artery. In the right antero-oblique angiocardiogram, the valvular pulmonary stenosis may be visualized. The main pulmonary artery is usually dilated. 3. Dye appears in the left ventricle and aorta by 1 to 1½ seconds. The appearance of the aorta is usually made one-half second after the pulmonary artery, and is light. An exception to this is Case 21 (Table 7), in which the aorta and the pulmonary artery filled simultaneously at 1½ seconds. However, the aorta was much lighter than the pulmonary artery. 4. The right auricle and ventricle appear markedly enlarged. The appendage of the right auricle is usually extremely dilated in the severe cases.

The patient in Case 21 (Table 7) was first seen shortly after birth, at which time she was markedly cyanotic and had to be in oxygen. By 3 weeks of age she had improved some and was well enough to be sent home. The other clinical features of the case are as follows: 1. Auscultation revealed a Grade III systolic murmur over the entire precordium. The second pulmonic sound was diminished. 2. Roentgenograms revealed an enlarged transverse diameter of the heart. There was elevation of the apex, straightening of the pulmonary area, and bulge of the right auricular region to the right. The left antero-oblique view showed an enlarged right auricle and ventricle. By 4½ months of age, the heart had enlarged more, mostly in the region of the right auricle and ventricle. 3. The pulmonary vascular pulsations were seen upon fluoroscopic examination. 4. The red blood cell count was 8,280,000; the hemoglobin concentration, 110%. 5. An electrocardiogram revealed left ventricular hypertrophy at 2 weeks of age, but by 4 months this changed and marked right auricular and right ventricular hypertrophy was shown. The cyanosis and dyspnea became worse between 4½ and 5 months. A clinical diagnosis of tetralogy of Fallot with an interauricular defect (pentalogy) was made.

Angiocardiography in the posteroanterior view gave the following findings: 1. Dye was shunted from the right auricle to the left auricle at one second (Fig. 11 *A*, Case 21). 2. The left ventricle, aorta, and pulmonary artery were seen simultaneously in 1½ seconds. However, the aorta was considerably lighter than the pulmonary artery (Fig. 11 *B*, Case 21). 3. The right auricle was markedly dilated. 4. Later reopacification of the right auricle occurred at 7½ seconds. This angiocardiogram was felt to be consistent with the diagnosis of pentalogy.

TABLE 7.—*Pulmonary Stenosis with Interauricular Communication*

Case	Age at Death, Mo.	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Surgery	Autopsy Findings
21	6	Pentalogy	Cyanosis since birth; Grade III systolic murmur; 2d pulmonic sound diminished; heart progressively enlarged; straight pulmonary area; right auricle and right ventricle enlarged; absent pulmonary vascular pulsations; ECG showed hypertrophy at 2 wk. of age, then changed to marked right auricular and right ventricular hypertrophy	Posteroanterior: shunt from right auricle to left auricle at 1 sec.; aorta and pulmonary artery seen at 1½ sec., along with right auricle, right ventricle; aorta much lighter than pulmonary artery; very large right auricle and right ventricle; compatible with diagnosis of tetralogy and interauricular septal defect (pentalogy)	Potts-Smith at 5 mo.; heart enlarged progressively until death 6 wk. later	Heart enlarged; markel pulmonary valvular stenosis; patent foramen ovale; marked enlargement of right auricle and right ventricle; status postaortic pulmonary anastomosis
22	8½	Pulmonary stenosis and septal defect	Cyanosis since birth; systolic murmur; marked progressive cardiac enlargement, both to right and left; lung fields clear; ECG showed marked right auricular and right ventricular hypertrophy	Posteroanterior: Film 1—large right auricle, right ventricle, left auricle, with large appendage, small pulmonary artery; Film 2—above and aorta Left antero-oblique: Film 1—tremendous right auricle and right ventricle; Film 2—right auricle, right ventricle, left auricle, and left ventricle, normal size pulmonary artery and light aorta	0	Pulmonary valvular stenosis; patent foramen ovale; interauricular septal defect; markel dilatation and hypertrophy of right auricle and right ventricle

Due to the rapid downhill course of the patient, a Potts-Smith operation was performed at 5½ months. In spite of an "initial improvement," the heart began enlarging rapidly two weeks postoperatively, and the patient died about three weeks postoperatively.

Autopsy findings were as follows: (*a*) marked valvular pulmonary stenosis, (*b*) patent foramen ovale (about 25% open), and (*c*) marked dilatation and hypertrophy of the right auricle and the right ventricle.

Although the diagnosis of pentalogy appeared reasonable by correlation of the clinical and angiocardiographic findings, this diagnosis proved erroneous. The angiocardiographic finding of simultaneous opacification of the aorta and pulmonary artery at 1½ seconds pointed to a dextroposed aorta. As mentioned previously, in pulmonary stenosis with an interauricular septal defect, the aorta usually does not appear until at least one-half second after the pulmonary artery. Considering that this case (Case 21) was so severe clinically, in retrospect it might be considered that the light aorta, although opacifying simultaneously with the pulmonary artery, is coming off the left ventricle entirely and is not dextroposed.

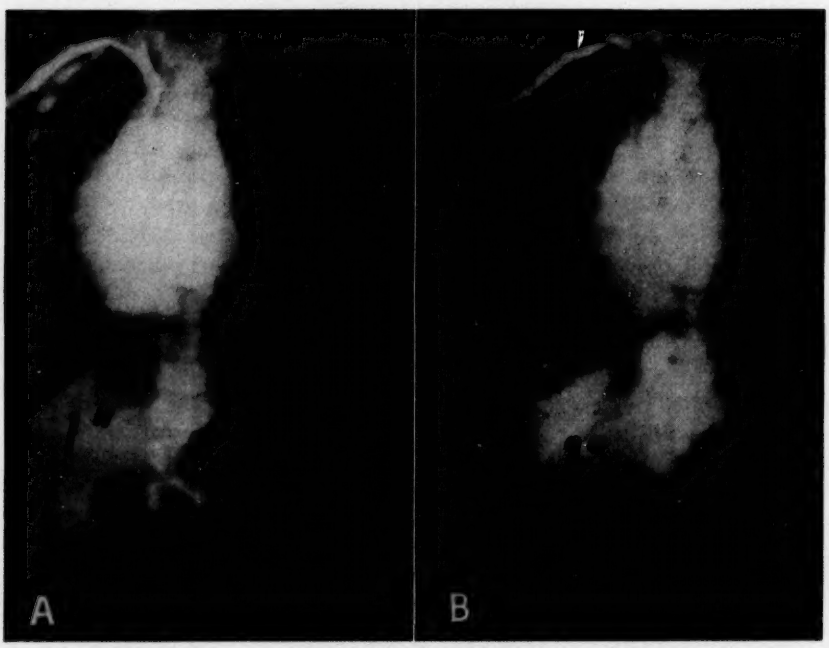

Fig. 11 (Case 21).—Pulmonary stenosis with interauricular septal defect. *A*, at one second the dye enters the left auricle from a huge right auricle. *B*, at two seconds the aorta and the pulmonary artery are visualized.

Case 22 (Table 7) is a typical severe case of this syndrome both clinically and angiocardiographically. The heart enlarged rapidly after birth, having a cardiothoracic ratio of 65% at 1 month of age, and 78% by 7 months of age. The right auricle, right ventricle, and left ventricle all appeared enlarged on roentgenograms.

There was a bulge in the pulmonary area and diminished pulmonary vascular pulsations. The electrocardiogram showed marked right auricular and right ventricular hypertrophy. The angiocardiogram showed an enlarged right auricle and ventricle, an enlarged left auricle and appendage, and a small pulmonary artery on the first film, the light aorta not filling until the second film.

B. *Noncyanotic Group.*—Persistent Atrioventricularis Communis (Table 8): This is a premature arrest in development in which the auricular and ventricular septa fail to meet. The tricuspid and mitral valves fuse, but there are large defects immediately above and below. A shunt of blood, therefore, occurs between the right and left auricles and the right and left ventricles, the predominant shunt being from left to right. This malformation usually occurs in a Mongolian idiot.

The patient in Case 23 was first seen at 2½ weeks of age. He had Mongolian facies as well as the other features of a Mongolian idiot. There was no visible cyanosis. A systolic murmur was heard, loudest at the apex. At one month of age, the chest roentgenograms showed a marked enlargement of the transverse diameter of the heart (cardiothoracic ratio of over 75%). The apex was elevated, the pulmonary area straight, and the right auricle very large. The left antero-oblique view revealed marked enlargement of the right auricle, the right ventricle, and the left ventricle; an electrocardiogram showed a horizontal heart with combined right and left ventricular hypertrophy. The clinical impression was a large atrioventricularis communis in a Mongol.

Angiocardiography in the posteroanterior view at one month of age showed a huge right auricle and a large appendage, the right ventricle, the left auricle and ventricle, and a large pulmonary artery and a large aorta, all at one second (Fig. 12 *A*, Case 23). All the chambers remained opacified and reopacified up to and including 10 seconds. The lungs were filled with a great deal of dye. This early filling of all four chambers along with the pulmonary artery and the aorta and the continuous reopacification of both sides of the heart are considered the characteristic angiocardiographic findings in this condition (Fig. 12 *B*, Case 23).

The infant did poorly clinically; diarrhea developed, and he died at 2 months of age. The anatomical diagnosis was as follows: (*a*) large atrioventricularis communis measuring 3 cm. in diameter, (*b*) marked dilatation of all chambers, particularly the right auricle and ventricle, (*c*) patent foramen ovale, (*d*) patent ductus arteriosus.

2. Interventricular Septal Defect: Two anatomical types of this malformation occur: the defect in the ventricular septum proper (Roger's disease) and the high interventricular septal defect which occurs in the membranous portion of the septum immediately beneath the aortic valve. This defect leads to a shunt of blood from the left ventricle into the right ventricle, since the pressure is much higher on the left. In the case of the high septal defect, blood may be shunted directly from the left ventricle into the pulmonary artery. This high defect may be almost indistinguishable from Eisenmenger's complex both clinically and pathologically.

The clinical features in a case of Roger's disease may consist only of a loud harsh systolic murmur in the left parasternal region, the rest of the cardiac study showing no significant abnormalities. However, in the case of a high septal defect, the clinical features may show distinct abnormalities besides the murmur. Cases 24 and 25 (Table 9) were both cases of high interventricular septal defects and

showed the following clinical features: 1. There was no cyanosis. 2. A harsh loud systolic murmur was heard. 3. There was an increased second pulmonic sound. 4. Roentgenograms revealed a slightly to markedly enlarged heart with a bulge in the pulmonary area and enlarged right auricle and right ventricle. 5. Fluoroscopy may reveal exaggerated pulmonary vascular pulsations. 6. Electrocardiograms revealed slight to marked right ventricular hypertrophy and also left ventricular hypertrophy in Case 24.

The angiocardiogram may be entirely normal in an interventricular septal defect with a small shunt of blood. In such cases it would be of no value as an aid to

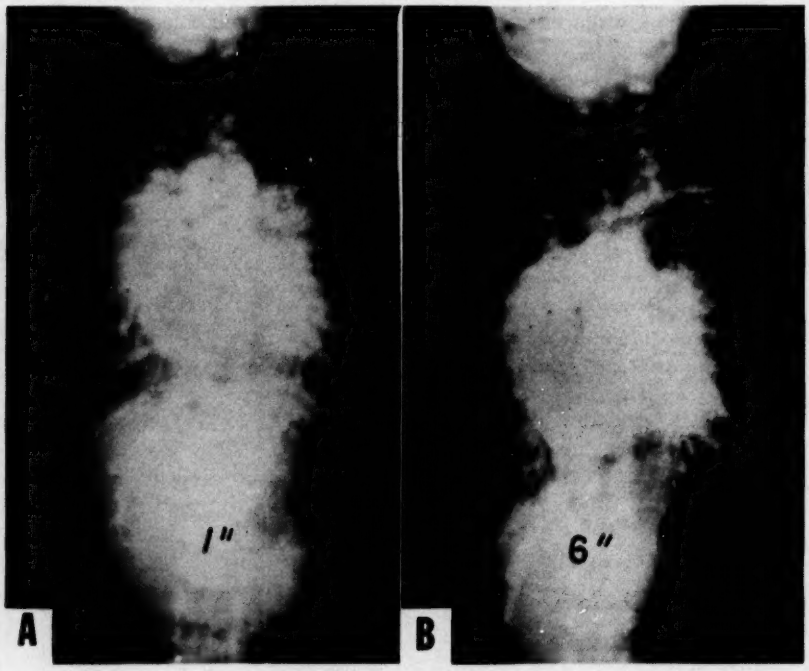

Fig. 12 (Case 23).—Persistent atrioventricularis communis. *A*, posteroanterior view. At one second simultaneous visualization of the right auricle and the right ventricle, the pulmonary artery, the left auricle, the left ventricle, and the aorta. *B*, posteroanterior view. At six seconds all chambers still filled with dye.

diagnosis, except for ruling out more severe disturbances. However, in high septal defects, such as the two cases mentioned in Table 9, the following findings may occur: Continuous reopacification of the right ventricle and the pulmonary artery due to the shunt of dye from the left ventricle into the right ventricle, or perhaps reopacification of the pulmonary artery alone when the shunt is directly from the left ventricle into the pulmonary artery.

3. Interventricular Septal Defect and Interauricular Communication: The combination of a high interventricular septal defect and either a large interauricular septal defect or a large patent foramen ovale has been noted to produce a rather distinctive clinical syndrome in four infants, all of whom died at under 6 months

TABLE 8.—*Persistent Atrioventricularis Communis*

Case	Age at Death, Mo.	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Autopsy Findings
23	3	Atrioventricularis communis	No cyanosis; systolic murmur at apex; large right auricle, right ventricle, and left ventricle; ECG showed combined heart strain	At 1 sec.: simultaneous visualization of right auricle, right ventricle, pulmonary artery, left auricle, left ventricle, and aorta At 6 sec.: all chambers still filled with dye	Large atrioventricularis communis; marked dilatation of all chambers, particularly right auricle and right ventricle; patent ductus arteriosus; interventricular defect, 3 cm. diameter; patent foramen ovale

TABLE 9.—*Interventricular Septal Defect*

Case	Age at Death, Mo.	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Autopsy Findings
24	5	Probable interauricular and interventricular septal defects	Not cyanotic; harsh systolic murmur; 2d pulmonic sound increased; heart enlarged progressively with bulge in pulmonary area; increased pulmonary vascular markings; enlarged right auricle, right ventricle; ECG showed combined heart strain	Posteroanterior: large right auricle and appendage; pulmonary artery very large; reopacification of right auricle, right ventricle, and pulmonary artery at 5 sec. Left antero-oblique: pulmonary artery very large; continuous reopacification of tremendous pulmonary artery	Interventricular septal defect (high); patent ductus botalli
25	3	Interventricular septal defect; gastroenteritis with massive gastrointestinal bleeding	No cyanosis; harsh systolic murmur; heart slightly enlarged; ECG showed slight right ventricular hypertrophy	Left antero-oblique: reopacification of right ventricle, right auricle (?), and pulmonary artery at 4-6½ sec.	Interventricular septal defect; patent foramen ovale

of age (Table 10). This is not the same as an atrioventricularis communis, as the defects are separate in the former. The abnormal circulation consists of large shunts of blood from the left auricle to the right auricle and from the left ventricle to the right ventricle. There is probably some reversal of the shunt from right to left also.

A summary of the clinical features of the four cases presented includes the following: 1. There was no cyanosis. 2. A harsh Grade IV systolic murmur was heard, accentuation of the second pulmonic sound. 3. The heart was moderately to markedly enlarged on roentgenograms in all but one case (Case 27). The left antero-oblique projection shows marked right auricular and ventricular enlargement, as well as some left ventricular enlargement. On posteroanterior projection there may be a bulge in the pulmonary area. 4. Electrocardiogram shows marked right auricular and ventricular hypertrophy or combined heart strain. 5. Fluoroscopy reveals normal to increased pulmonary vascular pulsations.

The angiocardiographic findings in this syndrome are as follows: 1. A large right auricle, right ventricle, and pulmonary artery are shown. 2. There is continuous reopacification of the right auricle, right ventricle, and pulmonary artery. 3. If a very large interauricular defect is present, as in Case 26 (Table 10), an early shunt of dye from the right auricle to the left auricle may occur, causing early opacification of the left auricle and ventricle and the aorta.

The youngest patient, with the most severe of the four cases presented, is Patient 26. This patient was first seen at 5 weeks of age with left and right heart failure. The outstanding clinical feature was that, although he was not clinically cyanotic, his heart was tremendously enlarged (cardiothoracic ratio of 70%). All chambers were enlarged on the roentgenograms and the electrocardiogram showed combined heart strain, predominantly right. The pertinent angiocardiographic finding in his case was that the left auricle and ventricle, and the aorta visualized early at 1½ seconds, and then the entire heart remained opacified until 8 seconds (Figs. 13 *A* and *B*, Case 26).

4. Coarctation of the Aorta: There are two types of coarctation anatomically, the infantile and the adult. The infantile type of coarctation occurs proximal to the isthmus of the aorta. In this type there is a large patent ductus leading from the pulmonary artery into the descending aorta just distal to the coarctation. The adult type is located distal to the isthmus of the aorta and there is usually no patent ductus arteriosus. The two types may be combined, in which case the coarctated segment extends from the proximal to the distal side of the isthmus and there is a patent ductus. Both cases presented in Table 11 are examples of combined infantile and adult types of coarctation.

In the adult type of coarctation, the coarctated segment is distal to the aortic isthmus and the left subclavian artery. Therefore, there is often a hypertension in the upper extremities and decreased or absent blood pressure in the lower extremities. Usually the clinical picture develops slowly, and the patient may not have any symptoms until later childhood, puberty, or adulthood, when usually the first symptom will be headache. Physical examination then reveals a moderate to marked hypertension in the upper extremities. The femoral pulsations are always diminished or absent. Upon recording the blood pressure in the lower extremities, it is found to be definitely lower than in the upper extremities. Thus the diagnosis can be made and should be made without laboratory aids. The chest roentgenograms may show some enlargement of the left ventricle with a prominent aortic knob. Notching of

TABLE 10.—*Interventricular Defects with Interauricular Communication*

Case	Age at Death	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Autopsy Findings
26	6 wk.	Atrioventricularis communis	No cyanosis; Grade IV systolic murmur; heart greatly enlarged; rales in lungs, liver enlarged; right auricle, right ventricle, left ventricle all enlarged; ECG showed combined heart strain, mostly vertical	Posteroanterior: left auricle, left ventricle, aorta at 1½ sec.; continuous reopacification of both sides of heart; heart remains full Left antero-oblique: left auricle filled at ½ sec.; aorta seen at 1½ sec.; entire heart filled as on posteroanterior view	Large interauricular septal defect; high interventricular septal defect; marked dilatation of right auricle; hypertrophy of right ventricle; slight left ventricular hypertrophy; slight dextroposition of aorta (?)
27	4 mo.	Interauricular or interventricular septal defect	No cyanosis; loud systolic murmur; heart normal size with bulge in pulmonary area; ECG showed right auricular and right ventricular hypertrophy	Posteroanterior and left antero-oblique: tremendous right auricle, large pulmonary artery; continuous reopacification of right auricle, right ventricle, and pulmonary artery	Large interauricular septal defect; small high interventricular septal defect; right ventricular hypertrophy
28	4 mo.	Interventricular septal defect	No cyanosis; loud systolic murmur; heart markedly enlarged, straight pulmonary area, enlarged right auricle, right ventricle, left ventricle; ECG showed combined heart strain	Posteroanterior: very large pulmonary artery; reopacification of right auricle, right ventricle, and pulmonary artery	Patent foramen ovale; interventricular septal defect; hypertrophy and dilatation of right ventricle and left ventricle
29*	2 mo.	Septal defect	No cyanosis; loud systolic murmur; 2d pulmonic sound increased; heart enlarged; bulge in pulmonary area; ECG showed probable left ventricular hypertrophy	Left antero-oblique: large pulmonary artery; continuous reopacification of right ventricle and large pulmonary artery Posteroanterior: normal	Patent foramen ovale; high interventricular septal defect; left ventricular hypertrophy; slight dextroposition of aorta (?)

* Died within 48 hr. following angiocardiography; thought to be a result of the procedure.

TABLE 11.—*Coarctation of the Aorta*

Case	Age at Death	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Autopsy Findings
30	2 yr.	Coaretation of aorta	Systolic and early diastolic murmur over base; femoral pulsations weak; blood pressure in arms 132/50; enlargement of left auricle and left ventricle; ECG showed bundle branch block and combined hypertrophy	Left antero-oblique: coaretation visualized beyond subclavian artery at 5 sec.; continuous reopacification of pulmonary artery consistent with patent ductus arteriosus Retrograde aortagraphy:* marked coaretation 2 cm. long seen beyond left subclavian artery	Coaretation of aorta, combined infantile and adult type; hypertrophy of both ventricles; patent ductus arteriosus
31	6 wk.	Coaretation of aorta, infantile and adult type	No cyanosis; no cardiac murmur; signs of cardiac decompensation; marked enlargement of heart, both right and left sides; femoral pulsations absent; blood pressure left arm 0/0, right arm 132/0; ECG showed combined right ventricular and left ventricular hypertrophy	Left antero-oblique: coaretation seen beyond left subclavian artery at 5 sec.; reopacification of pulmonary artery at 5-7½ sec.; enlarged right ventricle at 1 sec.	Coaretation of aorta, combined infantile and adult type; coaretated segment extends from proximal to distal side of aortic isthmus and patent ductus in this coaretated segment

* Patient died after this procedure.

the ribs will be seen if the patient is old enough. The electrocardiogram will show a moderate to marked left ventricular hypertrophy as the condition progresses.

The pathologic physiology and clinical features of infantile coarctation are quite different from the above. Since the coarctated segment is proximal to the isthmus of the aorta and, therefore, to the entrance of the ductus arteriosus, the circulation of the blood is as follows: Some of the blood flows through the heart as usual, leaves the left ventricle, and meets the obstruction in the arch of the aorta. Therefore there is hypertension in the upper extremities, hypotension in the lower part

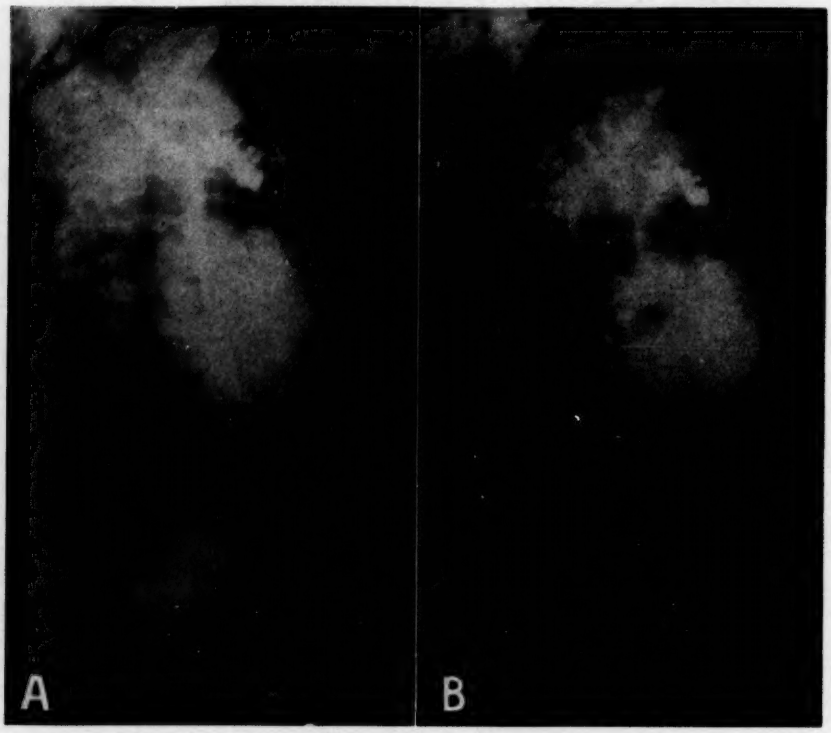

Fig. 13 (Case 26).—Interventricular and interauricular septal defects. *A*, at 1½ seconds, the entire heart is opacified. *B*, at eight seconds, opacification of all chambers.

of the body. However, some of the blood (unoxygenated) which leaves the right ventricle will flow directly from the pulmonary artery through the patent ductus arteriosus into the low-pressure descending aorta, distal to the coarctation, thence to the lower extremities. Thus the right ventricle pumps a great deal of blood into the descending aorta to the lower extremities. The right ventricle, therefore, undergoes rapid dilatation and hypertrophy, leading to rapid enlargement of the heart in the early weeks or months of life in the severe case. The left ventricle also hypertrophies, thus leading to combined hypertrophy. Because of unoxygenated blood entering the systemic circulation from the right ventricle, there may be lower oxygen saturation in the lower extremities than in the upper ones. The clinical

features of this syndrome, therefore, are as follows: 1. There is a rapid onset of dyspnea early in life. 2. There is usually a systolic murmur over the precordium. 3. Usually no cyanosis is present, although there may be a slight cyanosis of the toes. 4. Palpation of the femoral pulsations reveal them to be weak, but usually not absent. 5. Blood pressure in the lower extremities is lower than in the upper extremities. 6. Enlargement of the heart is seen in roentgenograms in the early weeks and months of life. The heart may become of tremendous size, as in Case 31 (Table 11). The left antero-oblique roentgenogram reveals marked enlargement of the right ventricle, as well as some enlargement of the left. 7. The electrocardio-

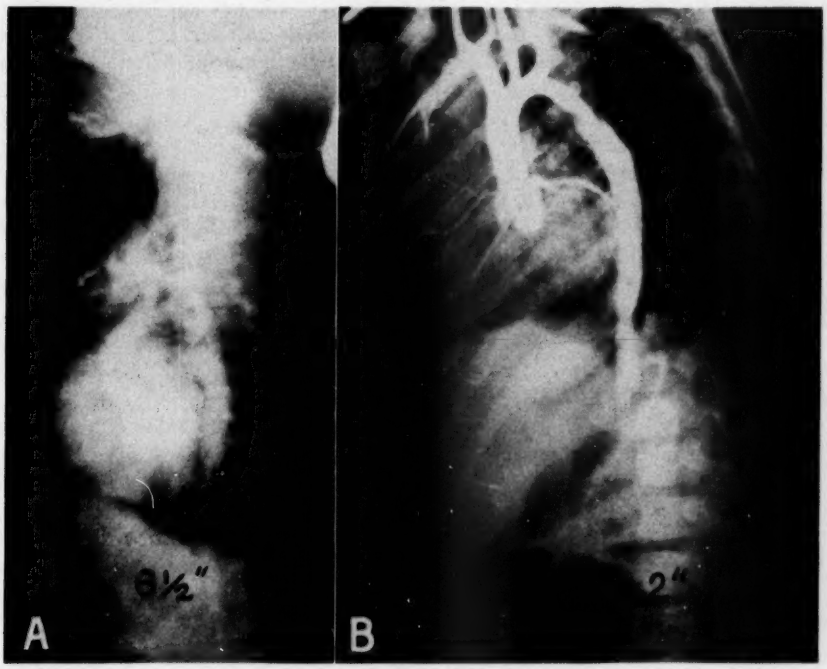

Fig. 14 (Case 31).—Coarctation of the aorta. *A*, at 6½ seconds, the left ventricle, the aorta, and the coarctation are visualized. *B*, retrograde aortography: The coarctation is well visualized, but the patent ductus arteriosus is not opacified. Note also the coronary arteries.

gram usually reveals right ventricular hypertrophy or combined ventricular hypertrophy. It will be noted in Table 11 that both cases present some of the above features.

Angiocardiography best visualizes a coarctation in the left antero-oblique projection. It should be visualized in the later films after the aorta opacifies. However, because of the dilution of the dye by this time, the outline of the defect may be hazy. Retrograde aortography may then be attempted in order to visualize the defect more perfectly. However, we have found this procedure difficult and dangerous in young infants. In both Case 30 and Case 31 the coarctation appears to be beyond the isthmus of the aorta (Fig. 14 *A* and *B*, Cases 30 and 31). However, in both

cases autopsy revealed the coarctated segment extending from an area proximal to the isthmus to one distal to it with the patent ductus arteriosus going into the coarctated segment in both cases. In Case 30 the patient died following the retrograde aortography, which failed to show the patent ductus arteriosus. In Case 31 the patient died in right and left heart failure.

It should be emphasized that coarctation of the aorta should be diagnosed in every case by clinical means, i. e., palpation of the femoral pulses and noting the blood pressures in the lower extremities is lower than in the upper extremities. Angiocardiography is not necessary for the diagnosis. However, it may be of aid to the surgeon in localizing the coarctation.

5. Endocardial Fibroelastosis: This congenital malformation has been recognized pathologically only in the past few years and has been correlated with a clinical syndrome only recently. We believe that these are the first two cases to be published with angiocardiographic findings.

The pathology of this condition consists of a thickening of the endocardium of the heart, predominantly at the left ventricle, produced by an increased size and number of elastic fibers as well as an overgrowth of fibrous tissue. There is associated deformity of the valves, usually affecting the mitral and aortic valves. The heart is markedly enlarged with the left ventricle showing a greater degree of hypertrophy and dilatation than the right. The cause of this condition has been the subject of much controversy. In the past it was thought to be the end result of a fetal endocarditis, but now it is believed that it is a primary defect in the endocardium with an overproduction of fibrous and elastic tissue, leading to an interference with circulation through the intraluminal vessels in the myocardium and, thereby, producing rapid dilatation and hypertrophy of the heart.

The clinical picture is not distinctive. In our cases studied (Table 12, plus three other cases studied clinically and pathologically in which angiocardiography was not performed), the following clinical features have been outstanding: (*a*) no cyanosis, (*b*) the onset of dyspnea within the first months of the first year of life, (*c*) a loud systolic murmur over the precordium, and (*d*) roentgenograms reveal marked generalized cardiac enlargement. In Case 32 the heart reached a tremendous size before death, the cardiothoracic ratio being 80%. The cardiothoracic ratio in Case 33, when the patient was 2½ months of age, was 70%. No definite individual chamber enlargement could be noted. Fluoroscopy revealed normal pulmonary vascular pulsations as far as could be determined. The electrocardiogram revealed marked left heart strain. Because of the inversion of all the T waves in both Case 32 and Case 33, it was difficult to differentiate the electrocardiogram from a similar one produced by an anomalous left coronary artery. This picture, correlated with the rapid and tremendous enlargement of the heart without cyanosis, led to the clinical diagnosis of aberrant left coronary artery arising from the pulmonary artery (Bland-White-Garland syndrome).[12]

Angiocardiography was performed in both cases. In Case 32 the circulation through the right side of the heart appeared normal. However, at 5 seconds, a left auricle with a very large appendage and a tremendous left ventricle with a thick wall and reopacification of the pulmonary artery was noted (Fig. 15 *A*, Case 32).

12. Gasul, B. M., and Loeffler, E.: Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery (Bland-White-Garland Syndrome): Report of 4 Cases, Pediatrics **4**:498-507, 1949.

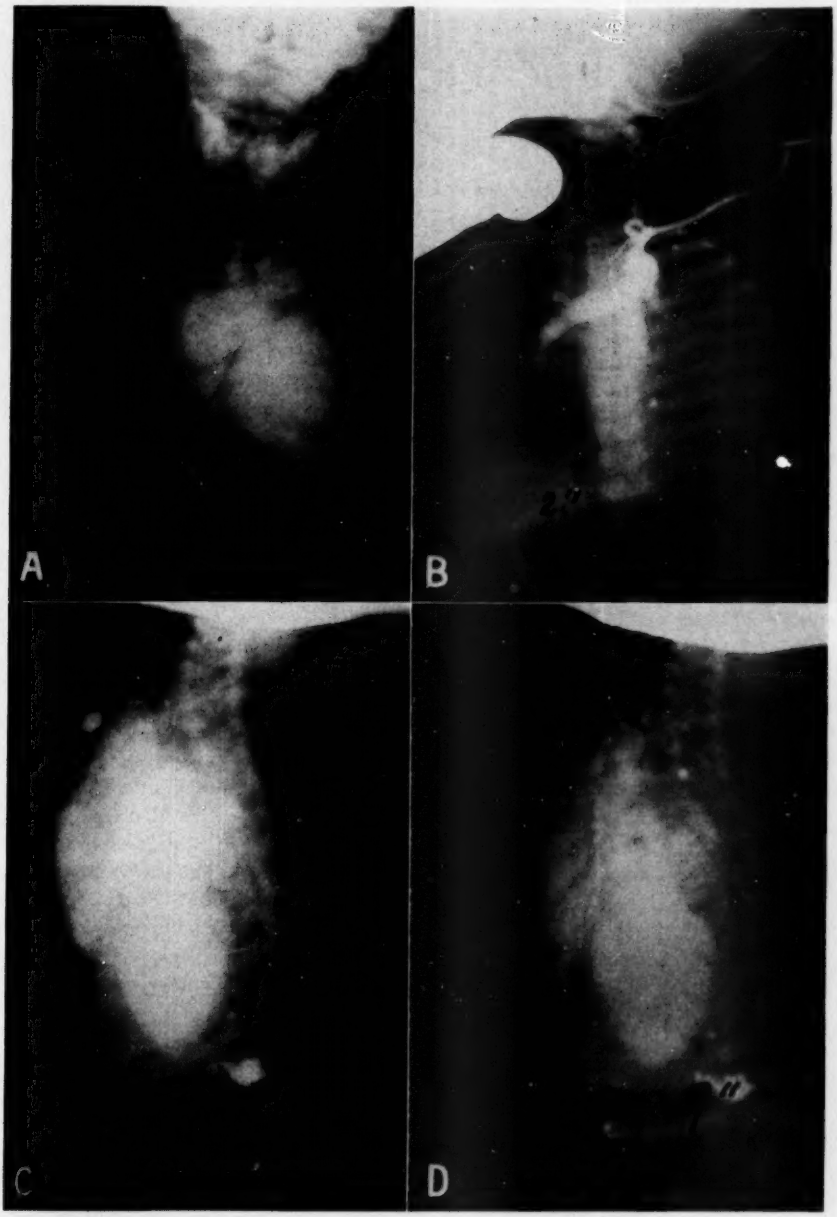

Fig. 15 (Case 32).—Fibroelastosis. *A*, at 5½ seconds, the left auricle with its appendage and the left ventricle are visualized. *B*, retrograde aortography: Simultaneous visualization of the aorta and the pulmonary artery. *C*, asystole of the left ventricle at 4½ seconds. *D*, asystole of left ventricle at nine seconds.

TABLE 12.—*Endocardial Fibroelastosis*

Case	Age at Death, Mo.	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Autopsy Findings
32	14	Aberrant left coronary artery off pulmonary artery; fibroelastosis and patent ductus arteriosus	Loud systolic murmur; no cyanosis; markedly enlarged heart, generalized; signs of cardiac decompensation; ECG showed left heart strain with inversion of T waves in standard leads	Posteroanterior: marked enlargement of pulmonary artery; continuous reopacification of pulmonary artery; marked enlargement of left auricle and left ventricle Retrograde aortography: shunt seen from aorta into pulmonary artery	Fibroelastosis; marked hypertrophy and dilatation of left auricle and left ventricle; patent ductus arteriosus
33	3	Aberrant left coronary artery of pulmonary artery; fibroelastosis	Marked dyspnea; no cyanosis; Grade IV systolic murmur over precordium; marked generalized cardiac enlargement; left heart strain on ECG; T waves all inverted	Left antero-oblique: enlarged left auricle and left ventricle; remains in diastole from 6 sec. (cardiac standstill); continuous opacification of pulmonary artery	Heart markedly enlarged; left ventricle markedly dilated and hypertrophied; endocardium of left ventricle thickened; aortic cusps thickened and deformed; mitral leaflets thickened; ductus closed; foramen ovale closed

TABLE 13.—*Eisenmenger's Complex*

Case	Age at Death, Mo.	Clinical Diagnosis	Basis for Clinical Diagnosis	Angiocardiographic Findings	Autopsy Findings
34	4½	Probable interauricular septal defect	No cyanosis; enlargement of right ventricle; Grade IV systolic murmur all over precordium; ECG showed right ventricular hypertrophy	No dextroposition of aorta in posteroanterior or right antero-oblique views; normal size pulmonary artery; reopacification of right auricle	Interventricular septal defect; interauricular septal defect; overriding aorta; hypertrophy and dilatation of the right ventricle and right auricle; normal size pulmonary artery

This was interpreted as a patent ductus arteriosus with left auricular and left ventricular enlargement too great to be accounted for merely by the patent ductus. The aortic-pulmonary shunt was confirmed by retrograde aortography (Fig. 15 *B*). The left antero-oblique angiocardiogram in Case 33 (Table 12) also revealed marked enlargement of the left ventricle. From 4½ seconds on, the heart was in asystole, with the tremendous left ventricle in diastole (Fig. 15 *C* and *D*), at least until 9½ seconds. (The patient recovered from the procedure, however, after intracardiac injection of epinephrine.) There appeared to be reopacification of the pulmonary artery also in this case, but autopsy revealed no patent ductus arteriosus.

The autopsy findings are noted in Table 12. There is marked dilatation and hypertrophy of the left ventricle in both cases. In Case 33 there is also a deformity of the mitral and aortic valves.

The diagnosis of fibroelastosis during life is largely an elimination diagnosis. After all other causes of marked progressive cardiac enlargement in a noncyanotic infant have been ruled out, this must be considered. The most difficult condition from which to differentiate fibroelastosis is an aberrant left coronary artery coming off the pulmonary artery, as was seen in the two cases presented here. We now feel that a clinical point in differentiation is the presence of a loud murmur in fibroelastosis due to valve deformities, whereas in the other syndrome a murmur is usually absent or minimal. The only value of angiocardiography is to confirm the enlargement of the left ventricle and to rule out significant shunts as a cause of the cardiac enlargement.

6. Eisenmenger's Complex (Table 13): This malformation, described by Eisenmenger in 1897, differs from tetralogy of Fallot in that the pulmonary artery is either normal or dilated, instead of being stenotic or atretic as it is in the latter. Because of this, cyanosis does not usually appear until late childhood or early adult life.[13]

The outstanding clinical finding is absence of cyanosis in infancy and early childhood, even though the arterial oxygen saturation may be less than normal. There is usually a loud systolic murmur present, heard best over the base of the heart and transmitted over the precordium. The second pulmonic sound is loud. The fluoroscopic and roentgenographic examination reveals usually a normal or slightly enlarged heart with a straight or convex pulmonary area, and the pulmonary vascular pulsations are usually exaggerated. The electrocardiogram usually shows right ventricular hypertrophy. Angiocardiography usually reveals simultaneous opacification of a large aorta and of a large pulmonary artery without stenosis.

In the only case in our series that came to autopsy, Case 34, that of a 4½-month old Negro infant, there was no cyanosis present. There was a loud Grade IV systolic murmur present over the base of the heart. The pulmonary area was straight, and the vascular pulmonary markings were considered to be within normal limits. The electrocardiogram showed right ventricular hypertrophy. Angiocardiograms taken in the posteroanterior and right antero-oblique views failed to show the dextroposition of the aorta (Fig. 16 *A*). The pulmonary arteries were of normal size, and the lungs filled well with the sodium iodomethamate. There was

13. Taussig, H. B.: Congenital Malformations of the Heart, New York, The Commonwealth Fund, Oxford University Press, 1947.

reopacification of the right auricle and possibly of the right ventricle at five seconds (Fig. 16 *B*).

It may be impossible to differentiate some cases of Eisenmenger's complex, especially in infants and young children, from a high interventricular septal defect, not only clinically but even at autopsy. We considered Cases 26 and 29 (Table 10) as examples of high interventricular septal defects. Clinically there was no cyanosis, and the angiocardiogram failed to show dextroposition of the aorta. Since there is no pulmonary stenosis in these cases, the pressure in the right ventricle is probably considerably lower than in the left ventricle, and the shunt is, therefore, from the left ventricle into the right ventricle and the pulmonary artery. Even at

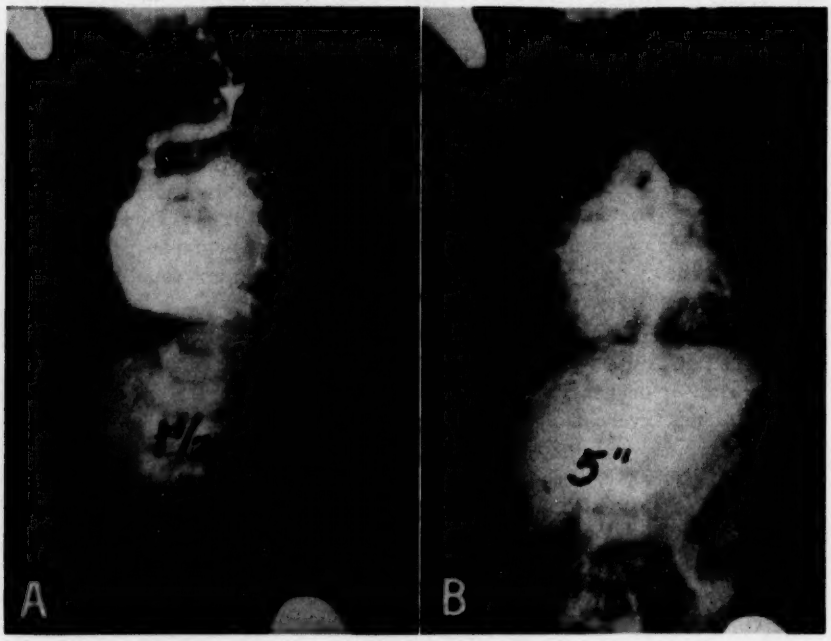

Fig. 16 (Case 34).—Eisenmenger's complex. *A*, a dextroposed aorta cannot be visualized at 1½ seconds. *B*, at five seconds, reopacification of the right auricle and of the right ventricle.

autopsy our pathologists were unwilling to commit themselves as to the presence or absence of a slight dextroposition of the aorta. We therefore feel on the basis of our findings that it may be impossible to differentiate clinically cases of Eisenmenger's complex in infants and young children from interventricular septal defects.

CONCLUSIONS AND SUMMARY

Based upon the correlation of angiocardiographic findings with clinical and pathologic findings in this series, the following conclusions may be stated regarding the value of angiocardiography as an aid to the clinical diagnosis of congenital cardiac malformations:

1. The procedure is effective in indicating intracardiac and extracardiac shunts and abnormalities in size, shape, and position of the great vessels, as well as of the

cardiac chambers, and in visualizing abnormalities in the return of the great veins to the heart.

2. Its greatest contribution is in the cyanotic group of malformations. Particularly in the young cyanotic infants, whose roentgenographic and electrocardiographic evidence may be difficult to interpret and in whom cardiac catheterization may be difficult or impossible, angiocardiography is most useful.

3. This procedure is of less value in the noncyanotic group of malformations, as left-to-right shunts are difficult to localize accurately. However, coarctation of the aorta is a noncyanotic condition which is effectively visualized.

4. It has been shown that angiocardiography was actually misleading in certain cases. Therefore one must be very careful in interpretation and aim only at correlating the angiocardiographic findings with the clinical findings, instead of making a completely independent angiocardiographic diagnosis.

5. It must be remembered that angiocardiography indicates only specific abnormalities of the heart, and therefore cannot be expected in itself to diagnose entire clinical syndromes. It must be viewed as merely another laboratory aid which is to be correlated with the history, physical examination, electrocardiography, roentgenography, and fluoroscopy and cardiac catheterization, in order to arrive at a final and more complete diagnosis.

6. In the great majority of cases of congenital malformations of the heart, the experienced clinician can make an adequate diagnosis with the conventional clinical aids. In practically all cases, he can decide by clinical means whether an operation is necessary. The value of angiocardiography, therefore, is to add corroborative evidence to the diagnosis in many cases, and to give the clinicians and surgeons a more exact picture of the abnormal anatomy and physiology involved.

7. Finally, from an academic standpoint, angiocardiography is of great value in furthering our understanding of the abnormal hemodynamics of congenital malformations of the heart during life. By correlating the angiocardiographic findings with the clinical syndrome and the pathologic findings, such as was done in this study, the clinician's understanding of the pathology present is improved and he is thus rendered more capable of diagnosing additional cases of the same type.

ADDENDUM

Since this article has been prepared for publication, 14 additional patients who have been studied clinically and angiocardiographically have come to autopsy. Nine of these belonged to the cyanotic group.

700 South Wood St., 12 (Dr. Gasul).

Acknowledgment of their help with this study is made to Dr. Samuel J. Hoffman of the Hektoen Institute for Medical Research, who is mostly responsible for the equipment and maintenance of the cardiophysiology department, to Dr. Henry G. Poncher, head of the Department of Pediatrics of the University of Illinois School of Medicine, whose co-operation made possible a study of a number of patients from the research hospital, to Dr. Morris Lev, consultant in pediatric pathology, to Dr. Hans Popper, Director of Pathology at the Cook County Hospital, to Dr. William Mavrelis and Dr. Paul Szanto, who performed the autopsies on these patients, and to Dr. L. B. Stewart, Dr. R. Casas, and Dr. C. Prec, for technical help in obtaining a number of the earlier angiocardiograms. Glenn Volz, chief technician, was of help during the entire five-year period of this study.

MEASLES ENCEPHALOMYELITIS

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THIS STUDY covers the incidence of measles encephalomyelitis in the city of Milwaukee over a 25-year period from 1927 to 1951 and incorporates the cases included in previous reports.[1] No attempt will be made to review the literature on measles encephalomyelitis, but we should like to call attention to various reports in the past few years which cover a significant number of cases. In 1949, Appelbaum, Dolgopol, and Dolgin[2] reported 74 cases, and in the same year Sawchuk, LaBoccetta, Tornay, Silverstein, and Peale reported 50 cases.[3] In 1950 Spragins, Shinners, and Rochester reported 31 additional cases.[4]

Numerous theories as to the cause of encephalomyelitis following rubeola have been advanced. Shaffer, Rake, and Hodes have suggested that this disease is due to the virus of measles.[5] Greenfield originated the theory that the measles virus activates another virus that is dormant in the patient and is responsible for the encephalitis picture.[6] Finley believes that measles encephalitis is an allergic response of the central nervous system to the measles virus.[7]

During the period from 1927 to 1951, 77 patients with measles encephalomyelitis were seen at the South View Hospital. The prevalence of measles during this 25-year period revealed the expected triannual peaks (Chart 1) with the incidence

From the Department of Internal Medicine, Marquette University School of Medicine, and the South View Hospital.

1. Peterman, M. G., and Fox, M. J.: Encephalitis as a Complication of Measles, Am. J. Dis. Child. **46**:512 (Sept.) 1933; Postmeasles Encephalitis, ibid. **57**:1253 (June) 1939.

2. Appelbaum, E.; Dolgopol, V. B., and Dolgin, J.: Measles Encephalitis, Am. J. Dis. Child. **77**:25 (Jan.) 1949.

3. Sawchuk, S.; LaBoccetta, A. C.; Tornay, A.; Silverstein, A., and Peale, A. R.: Measles Encephalitis, Am. J. Dis. Child. **78**:844 (Dec.) 1949.

4. Spragins, M.; Shinners, B. M., and Rochester, B.: Measles Encephalitis; Clinical and Electroencephalographic Study, Pediatrics **5**:599 (April) 1950.

5. Shaffer, M. F.; Rake, G., and Hodes, H. L.: Isolation of Virus from Patient with Fatal Encephalitis Complicating Measles, Am. J. Dis. Child. **64**:815 (Nov.) 1942.

6. Greenfield, J. G.: Pathology of Measles Encephalomyelitis, Brain **52**:171 (July) 1929.

7. Finley, K. H.: Pathogenesis of Encephalitis Occurring with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **39**:1047 (May) 1938.

of encephalomyelitis the greatest during these years (Chart 2). Known encephalomyelitis in relation to the prevalence of measles presents an incidence of 1.5 per 1,000.

This series included 38 women with 10 deaths, and 39 men, with 12 deaths, giving an over-all mortality rate of 28.6%. The ages of these patients varied from 5 months to 32 years, with 62.3% from 4 to and including 7 years of age (Chart 3).

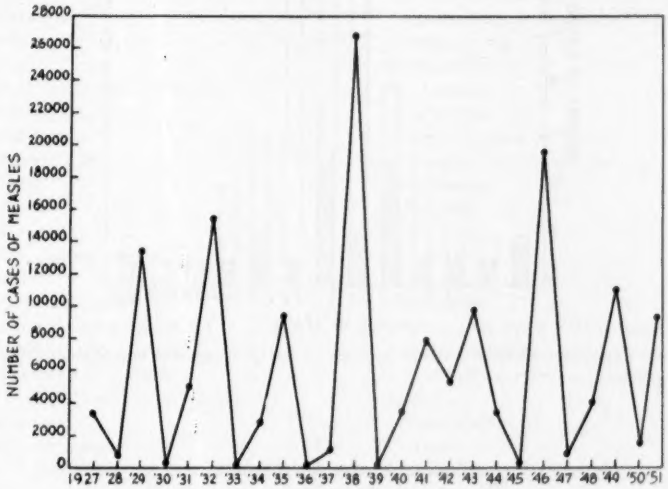

Chart 1.—Incidence of measles during the period from 1927 to 1951.

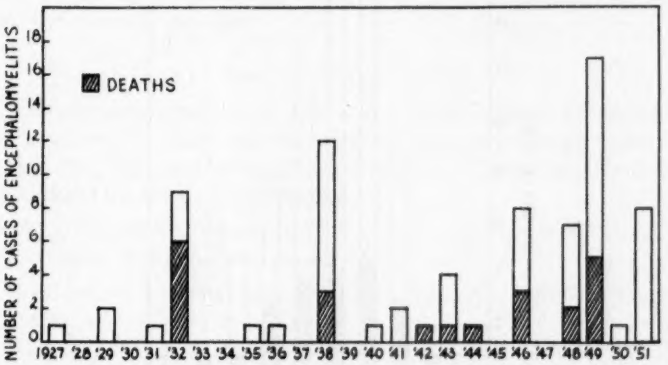

Chart 2.—Incidence of encephalomyelitis during the period from 1927 to 1951.

The onset of encephalomyelitis varied from several hours to nine days after the appearance of the morbilliform rash, with 46.7% occurring three to four days after the rash appeared (Chart 4). The rectal temperatures of these patients on admission to the hospital varied from 97.0 to 111.0 F., with 50% between 101.0 and 104.0 F. The temperature curves during hospitalization were not significant.

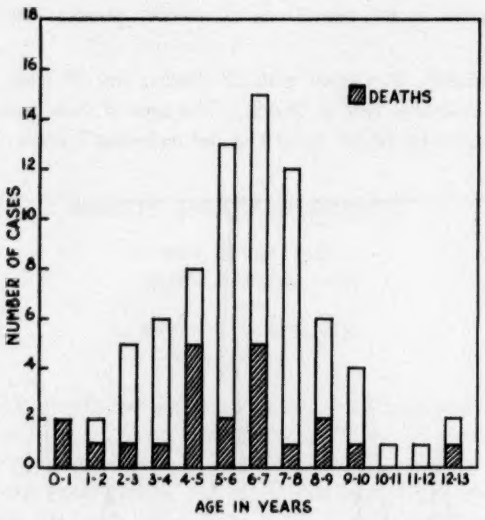

Chart 3.—Proportion of deaths to the number of cases of measles encephalomyelitis divided as to age groups.

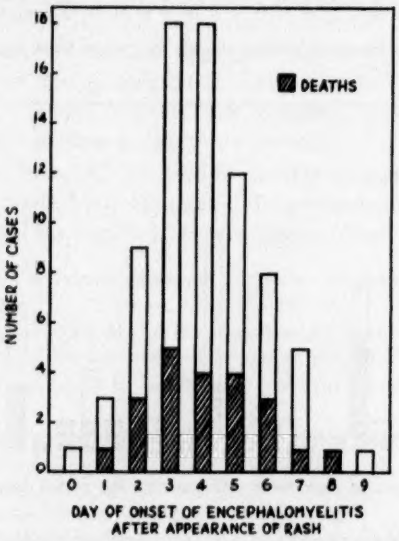

Chart 4.—Proportion of deaths to the number of cases of measles encephalomyelitis divided as to day of onset after appearance of rash.

We have charted the pertinent signs and symptoms in the manner of Appelbaum, Dolgopol, and Dolgin.[2]

Signs and Symptoms of Measles Encephalomyelitis During Hospitalization

A. Alterations in Sensorium		Carpopedal spasm	3
Coma	31	Hemiplegia	2
Drowsiness	21	Staggering gait	1
Stupor	15	E. Sensory changes	
Irritability	11	Pain in extremities	1
Restlessness	4	Hyperesthesia with sensory level	1
Delirium	3	F. Cranial nerves	
Apathy	1	Facial twitching	6
B. Signs of Meningeal Irritation		Nystagmus	4
Nuchal rigidity	32	Photophobia	4
Kernig sign	14	Fixed dilatation of pupils	4
Brudzinski sign	14	Absent reaction of pupils	2
Vomiting	12	Strabismus	1
Headache	7	Anisocoria	1
C. Reflexes		Epiphoria	1
Tendon reflexes absent	12	G. Muscle tone	
Babinski	12	Hypertonus	8
Cough reflex absent	57	Hypotonus	1
Tendon reflexes exaggerated	10	H. Bladder and bowel disturbances	
Abdominal reflexes absent	7	Urinary retention	1
Tendon reflexes sluggish	4	Urinary incontinence	1
D. Motor Power and Coordination		I. Medulla	
Convulsions	34	Hyperpyrexia	62
Spastic paraplegia	11	Cyanosis	11
Flaccid paraplegia	6	Cheyne-Stokes respiration	9
Tremors	5	J. Miscellaneous	
Choreiform movements	3	Aphasia	4

Of the 22 patients who died, eight had coma and convulsions, four had coma, and three had convulsions alone.

LABORATORY FINDINGS

The spinal fluid findings varied from 2 to 910 cells with 51.4% below 40 cells and 73.6% below 90. The majority of these cells were lymphocytes. Of the patients that died, 50% had spinal fluid counts above 90 cells, but this finding cannot be considered important prognostically.

In 61% of the patients the spinal fluid protein was increased. In all but two patients the spinal fluid sugar was normal or increased.

The blood leucocyte counts varied from 2,800 to 40,900, with 60% ranging from 9,000 to 18,000.

The percentage of neutrophiles was above 50% in 92% of the cases and above 75% in 47% of the cases.

OUTCOME

As stated before, 28.6% of our patients died. Of the remainder 65% answered a follow-up questionnaire concerning changes in disposition or personality following hospitalization, convulsive tendencies, disturbances in motor power or coordination, tremors or choreiform movements, disturbances in cranial nerve function, subsequent institutionalization, capabilities in schoolwork, and present health.

Twenty-two of the patients have recovered completely; one has displayed choreiform movements for one year with frequent headaches, dizzy spells, and vomiting since that time; one has had persistent tremors involving the extremities; one is epileptic; one has a residual cord bladder, foot drop, and myopia; one is poorly coordinated; three are mentally defective, and six have shown personality changes.

AUTOPSY FINDINGS

Five autopsies were done, and three with pertinent findings and brief case histories are described below. The first was that of a patient who died within 26 hours of the onset of encephalomyelitis; the second, one week after the onset, and the third, six months after the onset.

CASE 1.—T. C., 5 years of age, was admitted to the South View Hospital on June 15, 1949, with a history of the appearance of the typical morbilliform rash five days previously and the onset of coma two hours previously. On admission the patient was comatose with nuchal rigidity, Kernig sign, absent right patellar tendon reflex, absence of the pupillary reaction to light, and a rectal temperature of 105 F. He died 24 hours later.

Autopsy Findings.—The meningeal vessels were engorged. The white and gray matter of the brain substance was markedly soft, was edematous, and revealed prominence of the minute vessels. The ventricular system was normal in appearance. Marked dilatation and congestion of the vessels lining the ependyma and choroid plexus were present. The medulla and pons showed similar changes. The pituitary gland was small and normal in appearance.

Microscopic Findings.—In all sections there was a marked perivascular mononuclear and lymphocytic infiltration. Perivascular edema was present, and petechial hemorrhages were found in these areas. Marked perivascular demyelination was present. The vessels were dilated and congested. Chromatolysis and neuronophagia were present throughout.

Diagnosis.—Acute fulminating postinfectious measles encephalomyelitis was diagnosed.

CASE 2.—M. O'C., 4 years of age, was admitted to the South View Hospital on July 9, 1942, with a history of the appearance of the typical morbilliform rash on July 2, 1942, and generalized convulsions since July 4. On admission the patient was found to be stuporous and exhibited nuchal rigidity, Kernig sign, and Brudzinski sign. She died on July 11, 1942.

Autopsy Findings.—The brain was markedly swollen and large; the leptomeninges were raised in many places by accumulations of clear serous fluid; the surface vessels were distended and engorged. Serial section revealed marked perivascular edema. The left basal ganglia and the white matter of the right occipital lobe revealed areas in which the vessels appeared to be thrombosed. The ependyma was smooth and glistening.

Microscopic Findings.—There was generalized marked perivascular edema, particularly of cortex, basal ganglia, and cerebellum. Associated severe hyperemia with many areas of perivascular hemorrhages and marked vacuolization of cerebral tissue were noted. Perivascular areas revealed no cell accumulations, but diffuse polymorphonuclear infiltration was noted in the cerebrum and cerebellum.

Diagnosis.—The diagnosis was postmeasles encephalitis.

CASE 3.—G. L., 6 years of age, was admitted to the South View Hospital on April 19, 1949, with a history of the appearance of the typical morbilliform rash on April 17, 1949, and the onset of coma and convulsions several hours previously. The patient was comatose and had convulsions on admission, with bilateral Babinski and Hoffman signs, hypertension, and abdominal distention. The following day the temperature rose to 107 F. (rectal) and the convulsions continued in spite of drop ether. Repeat spinal taps were bloody on several occasions. Intermittent convulsions, twitching of the face and left arm, carpopedal spasm, coma, and pyrexia continued for six months. The patient experienced three separate episodes of bronchopneumonia which responded to antibiotics during this period. There were intermittent periods of slight elevation of the level of consciousness, and on Oct. 14, 1949, the previously noted spasm disappeared following fever of 108.6 F. (rectal). The patient died on Oct. 27, 1949.

Autopsy Findings.—The brain weighed 825 gm. The cerebral hemispheres were soft and fluctuant. The surface was congested throughout, and the leptomeninges were thickened and translucent. Thickening and fibrosis at the base of the brain rostral to the pons was present. There was atrophy of the gyri at the tip of the left occipital lobe. The ventricular system was distended throughout, and the surrounding gray matter was extremely thin. Multiple areas of softening were present, especially in the occipital lobes.

Microscopic Findings.—There was loss of brain substance in the superficial part of the cerebrum. Many foam cells were present in some areas. In others there were cysts and vacuole formation. Cellular degeneration and necrosis were prevalent. Many gemistocytic astrocytes were found. The vessels were greatly dilated and congested throughout. The cortical cells were sparse and greatly swollen.

Diagnosis.—Measles encephalomyelitis, chronic basilar meningitis and hydrocephalus, and bilateral bronchopneumonia was diagnosed.

The autopsy findings in the remaining cases in which the patients died were similar to those in Cases 1 and 2 above with perivascular demyelination, lymphocytic infiltration of the venous walls, passive congestion, minute cerebral hemorrhages, cerebral edema, and gliosis.

PATHOLOGY

We have studied the central nervous system in five autopsied cases of measles encephalitis. The study has failed to identify any characteristic lesion or constant distribution of lesions that might lead to a diagnosis of measles encephalitis. However, a number of observations have been recorded which suggest the diagnosis of this type of cerebral reaction.

The brain on gross examination reveals a universal marked hyperemia which is accompanied by accumulation of pools of fluid beneath the meninges. In most instances the cortical convolutions are flattened, and the brain frequently bulges through the incised dura. The imprint of the foramen magnum is prominent in most of the cases. Generally the brain is moderately increased in weight and variable in consistency, in some instances this being increased and in others decreased. The ependyma is deeply engorged, but the cerebral ventricles are not dilated. The meninges are glistening, and in none of the cases was there any cloudiness detected grossly.

Microscopic examination reveals a universal distribution of changes, perhaps more marked in the white substance of the hemispheres. There is severe congestion and both perivascular and pericellular edema. The perivascular spaces show frequent hemorrhage and variable cellular infiltrates. The perivascular cell accumulates consist principally of lymphocytes and histiocytes with occasional polymorphonuclear cells. At times these infiltrates are severe. About such areas the brain substance is very pale in staining and exceedingly spongy. In the white substance and in the cortex there are cellular infiltrations generally loosely arranged and consisting of an almost equal mixture of polymorphonuclear cells and histiocytes. These cell collections are not densely packed and are associated with considerable edema and loosening of the brain tissue of the area. Neuronal changes appear to be secondary and are present only in the areas of severe cellular infiltration where demyelination and loosening of the brain substance is pronounced. In contrast to poliomyelitis the cellular infiltrations and edema are seen principally in the cerebral hemispheres in which the cortex, white substance, and basal ganglia are chiefly affected. The pons shows similar changes and to a lesser extent changes are observed in the medulla and upper cord, but these are not associated with the

distribution of the nerve nuclei. The pituitary and pineal structures show only marked congestion and moderate edema.

COMMENT

The usual signs and symptoms leading to a diagnosis of measles encephalomyelitis are well known, but we believe that one of the earliest signs, that heretofore has received little emphasis, is the sudden cessation or depression of the typical measles cough. This finding was noted in 74% of our patients. The cough reflex depends upon stimuli from the respiratory epithelium passing along the afferent fibers of the vagus nerve through the nucleus of the tractus solitarius and thence along descending fibers to the spinal primary motor neurons and final discharge to the diaphragm, the intercostal and abdominal muscles, and the glottis. In measles encephalomyelitis involvement of the tractus solitarius will break this reflex arc with sudden cessation of coughing. In view of our observation, this sign during the active phase of rubeola should warn the observer of an impending encephalomyelitis when reinforced with other confirmatory signs of cerebral or spinal involvement.

We further stress that no medication containing codeine should ever be given to depress the cough of rubeola. We have observed instances of codeine intoxication that have occurred in the past two years. These patients were admitted to South View Hospital because of a supposed measles encephalomyelitis exhibiting convulsions, lethargy, vomiting, nuchal rigidity, cyanosis, and fever. In each instance the spinal fluid findings were normal, and the patient recovered completely within 24 hours after oxygen and helium therapy were instituted. Anoxia following the prolonged administration of codeine may well have been a factor.

The treatment of measules encephalomyelitis remains largely symptomatic. General anesthesia, barbiturates, magnesium sulfate, and hypertonic dextrose solutions all have been administered in an attempt to reduce cerebral edema and control convulsions. Convalescent serum has been of questionable value.

Certainly good supportive therapy and nursing care are essential to the welfare of these patients and do affect the ultimate mortality.

SUMMARY

Seventy-seven cases of measles encephalomyelitis are reported with a mortality rate of 28.6%.

Sixty-two per cent of the patients studied were between 4 and 7 years of age, inclusive.

The onset of encephalomyelitis occurred three to four days after the appearance of the morbilliform rash in 46% of the patients.

Coma or convulsions or both occurred in 68% of the patients who died.

A diminished or absent cough reflex was one of the earliest signs noted in 74% of the patients.

Where follow-up was possible, 61% of the patients have recovered completely.

Autopsy findings are reported in several cases.

The treatment of measles encephalomyelitis remains symptomatic.

Patients with codeine intoxication resembling measles encephalomyelitis are described, and the avoidance of medication containing codeine to depress the cough reflex in rubeola is stressed.

NEPHROTIC SYNDROME IN CHILDREN

Observations on the Clinical Course and the Influence of Sulfonamide and Antibiotic Therapy

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THIS STUDY was planned to analyze recent clinical experience and to determine the influence of sulfonamide and antibiotic therapy on the course of children with the nephrotic syndrome. The case histories of children with this condition who were admitted to the hospital from 1944 to 1950 were reviewed, and the course after discharge of each was studied. This time interval was chosen since it was during this period that intensive use was made of sulfonamides and antibiotics for this condition. No attempt will be made to review the literature, as this has been done thoroughly in recent articles.[1]

MATERIALS AND METHODS

The records of all children with the nephrotic syndrome admitted from 1944 to 1950, inclusive, were examined, and all the patients in this group still living in 1951 were reexamined. There were 29 such patients (aged 10 months to 6 years) admitted during this interval with the characteristic clinical signs and laboratory findings. These patients were followed either in the pediatric nephritis clinic or by their private physician.[2]

The urinary sediment [3] was examined daily while the patient was hospitalized and at frequent intervals in the clinic. Duration of hematuria was analyzed as follows: + indicates transient to

From the Kunstadter Laboratories for Pediatric Research, the Department of Pediatrics, Sarah Morris Hospital for Children, and Mandel Clinic of Michael Reese Hospital, Chicago. The Research Department is supported in part by the Chicago League for Nephritic Children and by the Michael Reese Research Foundation.

1. (*a*) Barness, L. A.; Moll, G. H., and Janeway, C. A.: The Nephrotic Syndrome: Natural History of the Disease, Pediatrics **5**:486-503 (March) 1950. (*b*) Schwarz, H.; Kohn, J. L., and Weiner, S. B.: Lipid Nephrosis: Observations over Period of 20 Years, Am. J. Dis. Child. **65**:355-363 (March) 1943. (*c*) Heymann, W., and Startzman, V.: Lipemic Nephrosis, J. Pediat. **28**:117-133 (Feb.) 1946. (*d*) Bradley, S. E., and Tyson, C. J.: Medical Progress: "Nephrotic Syndrome," New England J. Med. **238**:233 and 260 (Feb. 12 and 19) 1948. (*e*) Galán, E.: Nephrosis in Children, Am. J. Dis. Child. **77**:328-350 (March) 1949. (*f*) Barnett, H. L.; Forman, C. W., and Lauson, H. D.: The Nephrotic Syndrome in Children, in Advances in Pediatrics, edited by S. Z. Levine, and others, Chicago, The Yearbook Publishers, Inc., 1952, Vol. 5, pp. 53-128.

2. The authors are indebted to various private physicians for their excellent cooperation.

3. A uniform method of obtaining the sediment was followed. After a day on a diet with restricted fluids, a 12-hour night specimen was collected. A portion of this was centrifuged at 1,800 rpm for five minutes. An average of 2 erythrocytes or more per high power field in the sediment was considered evidence of hematuria.

one week; + +, two weeks to one month; + + +, one to two months; + + + +, longer than two months (Table 1).

Systolic blood pressures above 110 mm. or diastolic pressures above 70 mm. were considered abnormal. Most of the patients with hypertension had systolic pressures over 130 mm. and diastolic pressures over 80 mm. The duration of the hypertension was recorded as follows: + indicates transient to one week; + +, two weeks to one month; + + +, one to two months; + + + +, longer than two months (Table 1).

Determinations of serum urea nitrogen were made weekly in the hospital and at various intervals in the clinic. Values above 19 mg. per 100 cc. were considered abnormal.[4] The duration of azotemia was recorded as follows: + indicates transient to one week; + +, one to two weeks; + + +, two weeks to two months; + + + +, longer than two months (Table 1).

Only those infections which were of sufficient severity to require hospitalization or those acquired during hospitalization were reviewed and summarized. Mild upper respiratory disease was treated either at home or in the clinic.

In the final phase of the study, all children were reexamined whenever possible, a complete physical examination was made, and the following laboratory studies were completed: urinalysis; serum urea nitrogen, serum creatinine, serum cholesterol, and serum protein (albumin and globulin fractionation) determinations; kidney function tests (in those cases in which function was questioned), and a complete blood cell count.

The postmortem findings in the fatal cases were reviewed and causes of death determined when possible.

RESULTS

The results of the study are summarized in Tables 1 and 2. In the 29 cases reviewed, 19 (66%) of the patients were apparently well and showed no residual of disease; 2 were still in an active phase of the nephrotic syndrome without evidence of renal insufficiency; 2 had marked renal impairment, and 6 had died.

Hematuria.—Nine patients never had evidence of blood in the urine, and seven of these were well; two had died (the cause of death of both of these patients was acute bronchopneumonia). One patient had had hematuria lasting from one to two months, yet was apparently well in 1951. Eighteen patients had had hematuria lasting longer than two months at a time during the course of their illness. Of these 18, 10 were well, 2 were still in an active phase of the disease, 2 had evidence of renal insufficiency, and 4 had died (cause of death in 2 of the cases was renal failure and in the remaining 2, acute bronchopneumonia).

Azotemia.—Of 16 who had no evidence of urea nitrogen retention, 11 were well, 1 was still active, and 4 died (all primarily because of severe bronchopneumonia). Six had transient azotemia lasting no longer than one week, and all of these were well in 1951. Of three who had had azotemia lasting from one to two weeks at a time, two were well, and one still showed active signs of the nephrotic syndrome. Of four who had nitrogen retention lasting longer than two months, two died (cause of death was renal failure), and two had evidence of chronic nephritis in 1951.

Hypertension.—Of 19 patients who never showed an increase in blood pressure, 12 were well, 1 had evidence of renal insufficiency, and 2 still showed nephrotic signs. Four had died, all of acute bronchopneumonia. Four patients had transient hypertension (no more than one week), and these were well. Three patients had increased blood pressure lasting one to two weeks, and they were well. Of three patients who had had an increase in blood pressure lasting longer than two months, two were dead (cause of death was renal failure), and one showed evidence of renal insufficiency.

4. Conway, E. J.: Microdiffusion Analysis and Volumetric Error, Ed. 3, London, C. Crosby, Lockwood & Son, Ltd., 1951, pp. 152-167.

Intercurrent Infection.—Intercurrent infections of sufficient severity to require hospitalization developed in 23 of the 29 patients. They were treated with the newer drugs available during this period, predominantly sulfonamides or penicillin. These patients frequently had more than one hospitalization for infection (the total was 42 hospital admissions). The incidence of the more frequent infections was as follows: upper respiratory infections and otitis media, 18; bronchitis, bronchopneumonia, and lobar pneumonia, 14; peritonitis, 5, thrombophlebitis and cellulitis, 3; measles, 2.

COMMENT

Some investigators state that the differentiation between pure lipid nephrosis and the nephrotic syndrome is difficult, but that the distinction can be made if the patient is followed long enough.[5] In this study it was found more satisfactory and more in accord with the natural course to classify all patients exhibiting edema, proteinuria, lipemia, and hypoproteinemia as having the nephrotic syndrome, whether or not there was evidence of glomerulonephritis (hematuria, azotemia, and hypertension) at any time. Pure lipid nephrosis was therefore not differentiated from the nephrotic syndrome. When these patients were closely observed over a sufficient length of time many had hematuria at some time and/or transient periods of azotemia and hypertension. Furthermore, of the nine patients who did not have evidence of hematuria, azotemia, or hypertension, two died of fulminating infection, and both of these at autopsy showed evidence of glomerulonephritis. To illustrate the difficulty encountered in differentiating pure lipid nephrosis from the nephrotic syndrome as a stage of chronic glomerulonephritis the following protocols are presented.

Case 24 (Table 1).—A 21-month-old white boy was admitted to Sarah Morris Hospital for Children on May 19, 1948, because six days preceding admission generalized edema was noted with a resultant gain in weight. There was no history of preceding upper respiratory infection. On admission, urine examination revealed 4+ albumin, specific gravity 1.028, no red blood cells, no white blood cells, and only an occasional hyaline cast. The blood serum urea nitrogen was 11 mg. per 100 cc., creatinine 1.4 mg., cholesterol 300 mg., albumin 1.8 gm., and globulin 1.7 gm. per 100 ml. His blood pressure was 104/85. The findings on urinalyses remained essentially constant. During his hospital stay a right lower-lobe pneumonia developed, which was treated with penicillin and sulfonamides with good response. The patient was discharged July 10, 1948, in a fair state of remission. He was readmitted soon thereafter with findings suggestive of peritonitis and a recurrence of nephrotic signs. He was again given penicillin and sulfadiazine, with a favorable response. Urine revealed 4+ albumin with occasional red blood cells per high power field and frequently numbers of hyaline and granular casts; the serum urea nitrogen was 24 mg., total serum protein 3.6 gm. and albumin 0.3 gm. per 100 ml. Frequently the urinary sediment contained many red blood cells. The patient was discharged on Sept. 29, 1948, in fair condition. He was readmitted Oct. 26, 1948, because of anasarca and a right lower-lobe pneumonia and again given penicillin. Urine revealed 4+ albumin with 20 to 25 red blood cells per high power field and many casts. The serum protein concentration was 3.1 gm., albumin 0.1 gm., alpha globulin 1.8 gm., beta globulin 1.15 gm., and gamma globulin 0.05 gm. per 100 ml. The cholesterol level was 1,092 mg. per 100 ml. The patient was discharged Nov. 4, 1948, with mild edema and in fair general condition. He was readmitted Jan. 4, 1949, because of cellulitis of the right thigh and massive anasarca. The blood pressure at this time was 135/90. An abdominal paracentesis was done, and penicillin was given, with good response of the infectious process. The urine continued

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to reveal many red blood cells. Serum protein concentration was 3.1 gm. per 100 ml., albumin 0.3 gm., and globulin fractionation alpha 2.3 gm., beta 0.1 gm., and gamma 0.1 gm. per 100 ml. Serum cholesterol was 832 mg. per 100 ml. The patient was discharged on Jan. 23, 1949, clinically much improved. He was again readmitted April 1, 1949, because of cellulitis of both legs and marked edema. Penicillin was given again, and the infection subsided. Multiple paracenteses were necessary during this admission. There was no essential change in the blood or urine studies. Before discharge a marked diuresis occurred. The child was discharged in fair remission on May 18, 1949. He was readmitted Jan. 21, 1950, because of high temperature and convulsions. The blood pressure was 140/110. Cardiac failure developed, and he was given digitalis. The patient died of uremia and heart failure. Findings on urinalysis before death were as follows: albumin 4+; specific gravity 1.010; 20 to 50 red blood cells, 10 to 20 white blood cells, and many hyaline and granular casts per high power field; the blood serum urea nitrogen was 71.3 mg., creatinine 4.3 mg., and calcium 3.8 mg. per 100 ml. The postmortem findings are summarized in Table 1.

Case 19 (Table 1).—A 4-year-old Negro boy entered the hospital Oct. 12, 1947, with a history of intermittent swelling about the eyes for the previous three to four months. One day before admission generalized edema was noted. Blood pressure on admission was 150/90, and this returned to normal after three weeks. The patient was given 300 ml. of serum, and was given penicillin for a pharyngitis which developed during hospitalization. During the hospital stay urinalysis revealed a persistent 4+ albumin, occasional red blood cells, and 1 to 2 white blood cells per high power field; serum urea nitrogen was 9 mg., total protein 3.7 gm., albumin 1.8 gm., and cholesterol 346 mg. per 100 ml. The patient was discharged Nov. 14, 1947, edema-free. He was readmitted Nov. 30, 1947, with recurrence of edema and ascites and a blood pressure of 120/80. He was given a salt-poor high-protein diet and penicillin. During hospitalization urinalysis showed 4+ albumin with many casts and 10 to 15 red blood cells and 6 to 8 white blood cells per high power field. He was given serum without significant effect. A whole-blood transfusion was given because of anemia. The serum urea nitrogen was 40 mg., total protein 4.3 gm., albumin 1.8 gm., and cholesterol 552 mg. per 100 ml. The child, after three weeks, showed continued improvement, and he was discharged March 1, 1948, in fair remission. At the time of discharge his serum urea nitrogen was normal. He was readmitted May 27, 1948, because of anasarca associated with a pharyngitis and upper respiratory infection. The total serum protein concentration was 3.6 gm., albumin 1.3 gm., and serum urea nitrogen 85 mg. per 100 ml. The urinary sediment revealed occasional hyaline and granular casts, 60 to 80 red blood cells per high power field, and 4+ albumin. The general condition was extremely poor, and it was thought that he would soon die. The ascites was such as to cause respiratory embarrassment. Abdominal paracentesis gave considerable relief. His improvement thereafter was progressive, and he was discharged clinically improved on June 17, 1948. Serum urea nitrogen was 16 mg. per 100 ml., and the urine revealed albumin 4+, occasional casts, and 20 to 30 red blood cells per high power field. He was admitted again on Feb. 9, 1949, with a diagnosis of acute tonsilitis. Blood pressure was 112/70; urinalysis revealed 4+ albumin, occasional red blood cells and white blood cells per high power field, and no casts; serum urea nitrogen was 19 mg., total serum protein 5.8 gm., albumin 2.3 gm., and cholesterol 103 mg. per 100 ml. He responded well to penicillin and was discharged. The condition has remained in remission. One month after discharge from the hospital, there was no albumin in the urine and no cellular elements; the specific gravity was 1.023. Serum urea nitrogen was 15.6 mg., total serum protein 8.1 gm., and albumin 4.6 gm. per 100 ml. He has continued to do well and has remained symptom-free for two years.

These two patients demonstrate the difficulty in distinguishing between so-called pure lipid nephrosis and the nephrotic stage of chronic nephritis. The first patient described above might have been accepted on the first admission to have had a pure lipid nephrosis, yet progressive renal insufficiency developed; the second patient on first admission suggested considerable glomerular involvement, yet eventually appears to have recovered. A review of the cases presented and summarized in Tables 1 and 2 demonstrates that microscopic hematuria and azotemia were not

TABLE 1.—*Summary of the Case Study*

Case	Sex	Age at Onset, Yr.	Hospitalization	Hematuria	Azotemia	Hypertension	Intercurrent Infection	Therapy	Follow-Up
Case 1.....	F	4	6/19/44-1/16/45	++++	+	0	Thrombophlebitis and peritonitis	Sulfonamides and penicillin	After 1 mo., patient in remission and remained so; findings on urinalysis within normal limits; specific gravity 1.022; total protein 7.7 gm.; albumin 4.5 gm.; serum urea nitrogen 14 mg.; cholesterol 193 mg.
Case 2.....	F	1 1/12	6/10/48-10/24/48	++++	0	++	Upper respiratory infection and otitis media	Sulfonamides and penicillin	Patient continued to have albumin in urine ranging from 1-2+; specific gravity 1.026; patient remained in remission; after 11 mo. urine cleared; patient now doing well; total protein 6.2 gm.; albumin 3.4 gm.
			12/26/48-1/ 3/49	++++	0	0	.....	.....	
			3/ 3/49-4/12/49	0	0	0	Upper respiratory infection and bronchitis	Penicillin	
			10/31/49-11/ 9/49	0	0	0	Upper respiratory infection	Penicillin	
Case 3.....	F	3	9/22/47-10/10/47	+	0	0	Pharyngitis	Penicillin	Now in complete remission for 2 yr.; urine within normal limits; total protein 7.3 gm.; albumin 4.8 gm.; serum urea nitrogen 16 mg.; cholesterol 187 mg.
			12/15/47-1/15/48	+++	0	0	Patient contracted measles and had remission following attack	.....	
Case 4.....	M	1 1/2	10/24/46-11/ 6/46	++++	0	0	.....	.....	Patient at present doing well; since last discharge has shown progressive improvement; condition in remission 4 yr.; urine within normal limits; total protein 6.5 gm.; albumin 4.5 gm.; serum urea nitrogen 6 mg.; cholesterol 143 mg.
			11/28/46-12/23/46	++++	0	0	Upper respiratory infection and tonsillitis	Penicillin	
			12/31/46-1/ 8/47	++++	0	+	.....	.....	
Case 5.....	M	3	9/ 4/47-9/11/47	0	0	0	.....	.....	In good remission 1 mo. after discharge; patient well 3 yr.
			12/26/47-1/ 6/48	0	0	0	Tonsillitis	Penicillin	
Case 6.....	F	2	12/22/47-1/ 9/48	+	0	0	Lobar pneumonia	Sulfadiazine and penicillin	At present impending renal failure; urinary concentration 1.015; creatinine clearance test 40% of normal; serum urea nitrogen 87 mg.; serum creatinine 4.2 mg.; total protein 3.2 gm.; albumin 1.0 gm.; urine 4+ albumin with many casts, 1-3 red blood cells, 8-10 white blood cells per high power field
			10/ 6/48-10/13/48	++	+	0	Lobar pneumonia	Penicillin	
			8/28/50-9/ 5/50	++++	++++	0	.....	.....	

TABLE 1.—*Summary of Case Study—Continued*

Case	Sex	Age at Onset, Yr.	Hospitalization	Hematuria	Azotemia	Hypertension	Intercurrent Infection	Therapy	Follow-Up
Case 7.....	F	4	10/ 9/47-10/28/47	+++	0	++	.....	.....	Patient being seen at another clinic; impending renal failure; course revealed persistence of red blood cells in urinary sediment with casts and occasional white blood cells; patient now has chronic uremia with hypertension and poor urinary concentration
Case 8.....	M	3	11/ 7/47-12/ 4/47	0	0	0	Tonsillitis	Penicillin	Patient followed in another clinic; after 4 yr. of frequent recurrences associated with occasional azotemia and hematuria; he is now well with no renal impairment and has remained well for 1 yr.
Case 9.....	M	2	7/12/49-7/24/49	+	+	+	.....	.....	Well 2 mo. after discharge with no residual and has remained well for 2 yr.
Case 10.....	F	3	12/ 2/44-1/ 5/45	0	0	0	Tonsillitis	Sulfadiazine and penicillin	Patient had remission 3 mo. after discharge; has been asymptomatic since; urinary findings within normal limits
			3/11/45-3/16/45	0	0	0	Upper respiratory infection and tonsillitis	Sulfadiazine and penicillin	
Case 11.....	M	1¾12	3/30/48-4/24/48	++++	++	0	Left lower-lobe pneumonia	Penicillin	After discharge patient showed marked improvement and after 3½ mo. was well with no recurrences; urine within normal limits; serum urea nitrogen 14.6 mg.; total protein 7.1 gm.; albumin 4.7 gm.; blood pressure 102/60
			5/18/48-5/28/48	++	0	0	Pharyngitis and tonsillitis	Penicillin	
Case 12.....	F	2	6/28/46-7/11/46	0	0	0	Lobar pneumonia	Penicillin and streptomycin	Patient continued to have recurrences and remissions for 1 yr. with occasional hematuria; after 1 yr. had remission and has been well 2½ yr.; serum urea nitrogen 14 mg.; total protein 7 gm.; albumin 4.7 gm.; urine within normal limits
			1/ 6/47-1/25/47	++++	0	0	.....	.....	
Case 13.....	M	2½12	1/16/45-2/10/45	0	0	0	.....	.....	Spontaneous improvement 3 mo. after discharge; has been doing well for past 5 yr.; total protein 6.2 gm.; albumin 3.5 gm.; urine within normal limits
Case 14.....	M	6	7/21/49-8/ 4/49	++++	0	0	Pneumonia	Penicillin	Patient continued to show signs of disease for 6 mo., with hematuria intermittently; after this period he continued to show progressive improvement and has been asymptomatic; for past 1½ yr. urine within normal limits
			9/29/49-10/14/49	++++	0	0	.....	.....	

Case 15.....	M	10/12	3/15/49- 4/ 1/49	0	0	0	Upper respiratory infection	Penicillin	Patient well after discharge but continued to have albumin for 6 mo.; thereafter patient asymptomatic and doing well; urine within normal limits
Case 16.....	M	3	7/22/48- 8/13/48	0	+	0	.....	.....	Patient became symptom-free 6 mo. after discharge but continued to show albumin for 4 additional months and thereafter has been asymptomatic for 2 yr.; urine within normal limits
			9/28/48- 10/28/48	0	0	+	Otitis media	Penicillin	
Case 17.....	M	4	4/24/45- 6/23/45	0	+	0	.....	.....	After discharge continued to show albumin in urine for 4 mo. and thereafter asymptomatic for 5 yr.; urine within normal limits
			8/ 2/45- 8/15/45	0	0	0	.....	.....	
Case 18.....	M	3	4/19/49- 4/30/49	0	+	0	.....	.....	Many remissions and exacerbations for 6 mo. after discharge; thereafter continued to show improvement; patient continued to have albumin for 8 additional months and thereafter has been well 1 yr.; urine within normal limits; serum urea nitrogen 18 mg.; total protein 7.8 gm.; albumin 4.5 gm.
			6/ 6/49- 6/30/49	+	+	0	Pharyngitis	Penicillin	
			7/ 5/49- 8/13/49	++++	0	+	.....	.....	
			11/20/49- 11/27/49	++++	0	0	Pneumonia	Penicillin	
Case 19.....	M	4	10/12/47- 11/14/47	0	0	++	Pharyngitis	Penicillin	Patient after discharge remained in good remission; continued to show albumin in urine for 3 mo.; this cleared and patient has been well for 2 yr.; serum urea nitrogen 9 mg., total protein 8.1 gm.; albumin 4.6 gm.; urine within normal limits
			11/30/47- 3/14/48	++++	+	0	.....	.....	
			5/27/48- 6/17/48	++++	+	0	.....	.....	
			2/ 9/49- 2/17/49	0	0	0	Acute tonsillitis	Penicillin	
Case 20.....	M	2	11/20/45- 12/ 1/45	0	0	0	.....	.....	After last admission there has been a remission and he has remained well for 5 yr.; urine within normal limits; serum urea nitrogen 12 mg.; total protein 7.2 gm.; albumin 4.2 gm.
			12/21/45- 1/10/46	0	0	0	Acute otitis	Penicillin	
			2/13/46- 4/21/46	0	+	0	Peritonitis developed during hospital stay	Penicillin	
			5/14/46- 6/29/46	0	0	0	.....	.....	
			11/27/46- 12/20/46	0	0	0	Acute tonsillitis	Sulfadiazine	

TABLE 1.—*Summary of Case Study—Continued*

Case	Sex	Age at Onset, Yr.	Hospitalization	Hematuria	Azotemia	Hypertension	Intercurrent Infection	Therapy	Follow-Up
Case 21.....	F	3	10/13/49-11/29/49	++++	0	0	.....	.....	Patient during the first 2 yr. had frequent recurrences with intermittent periods of hematuria; on 7/9/51 measles developed; 3 mo. after this attack patient was symptom-free; urine within normal limits; specific gravity 1.026; total protein 7.2 gm.; albumin 4.1 gm.; cholesterol 200 mg.
Case 22.....	M	8½	9/ 9/49-10/ 6/49	++++	0	0	Right lower-lobe pneumonia with effusion	Penicillin and sulfadiazine	Since discharge patient has been edema-free except for occasional period of puffy lids; urine 4+ albumin; red blood cell 0; casts; specific gravity 1.025; total protein 3.8 gm.; albumin 0.6 gm.; serum urea nitrogen 14 mg.
			8/ 8/50-8/20/50	0	0	0	.....	.....	
Case 23.....	M	1911/12	9/ 9/49-10/ 6/49	++++	++	0	.....	.....	Patient being seen in neighboring town; has had frequent exacerbations and remission with period of azotemia and hematuria; urine reveals 4+ albumin
Case 24.....	M	1911/12	5/19/48-6/ 4/48	0	0	0	Right lower-lobe pneumonia	Sulfadiazine and penicillin	Patient demonstrated findings of a chronic nephritis with progression of symptoms and nitrogenous and phosphate retention; signs of cardiac failure and hypertensive encephalopathy developed and patient died; postmortem examination revealed the following: subacute glomerulonephritis; bronchopneumonia; cardiac hypertrophy; passive hyperemia of lungs, liver, spleen, and kidney; hydroperitoneum; cloudy swelling of heart, liver, and kidney
			8/12/48-9/29/48	++	+	0	Pneumococcal peritonitis	Penicillin	
			10/26/48-11/ 4/48	++++	0	0	Right lower-lobe pneumonia	Penicillin	
			1/ 4/49-1/22/49	++++	0	++++	Cellulitis of leg	Penicillin	
			4/ 1/49-5/18/49	++++	0	++++	Cellulitis of right and left thighs	Penicillin	
			1/21/50-4/20/50 (Death)	++++	++++	++++	.....	.....	
Case 25.....	M	3	3/23/49-3/30/49	0	0	0	.....	.....	Patient entered Sarah Morris Hospital with bronchopneumonia; cardiac failure developed and patient died soon after admission; postmortem examination revealed the following: acute glomerulonephritis superimposed upon a subacute glomerulonephritis; acute bronchopneumonia; cloudy swelling and interstitial edema of myocardium; cardiac dilatation; passive hyperemia of lungs, liver, spleen, and kidney; cholesterosis of left atrium; cortical edema of left suprarenal
			7/31/49-8/ 4/49	++++	0	0	.....	.....	
			9/10/49-9/11/49	++++	0	0	.....	.....	
			4/24/50-4/25/50 (Death)	++++	–	–	.....	.....	

Case 26.....	M	4	7/ 7/44-7/16/44	0	0	0	.....	.....	Postmortem examination revealed the following: bilateral bronchopneumonia; pulmonary edema; subacute glomerulonephritis; hydrothorax; chronic interstitial myocarditis; chronic peptic ulcer of duodenum
			7/22/44-5/13/45	++++	0	0	Pharyngitis	Sulfadiazine and penicillin	
			9/15/45-10/14/45	0	0	0	.....	.....	
			11/28/45-12/ 6/45	0	0	0	Upper respiratory infection	Sulfadiazine and penicillin	
			12/25/45-1/ 2/46 (Death)	0	0	0	Bronchopneumonia	Penicillin	
Case 27.....	M	?	6/29/47-7/23/47 (Death)	0	0	0	Patient on prophylactic penicillin regimen because of frequent upper respiratory infections	.....	Bronchopneumonia developed and patient died; postmortem examination revealed the following: proliferative glomerulonephritis; general anasarca; bilateral bronchopneumonia; edema and dilatation of heart; acute passive hyperemia of liver; subendocardial cholesterol deposits
Case 28.....	M	2	9/28/44-12/ 2/44 (Death)	0 at onset. 2 months before demise had red blood cells in urinary sediment	0	0	Peritonitis and bronchopneumonia developed	Penicillin and sulfadiazine	Patient died; permission for postmortem examination refused
Case 29.....	M	3	1/31/44-4/10/44	0	0	0	Bronchopneumonia	Sulfonamides and penicillin	Signs of chronic nephritis developed; patient treated at another clinic and died 6 mo. following last admission; permission for postmortem examination refused; cause of death uremia
			8/13/45-9/18/45	0	0	0	Left lower-lobe pneumonia	Penicillin	
			2/19/48-3/ 6/48	.....	0	0	.....	.....	
			3/21/48-4/ 9/48 (Death, 9/23/48)	++++	++++	++++	.....	.....	

infrequent findings in the course of the disease. Ten of the patients studied who persistently demonstrated long and/or recurrent periods of hematuria and/or azotemia are now well.

Presented with a patient suffering with the nephrotic syndrome a more important consideration is to determine which child will and which will not recover, rather than to differentiate between two dubiously separate entities. Making a differential diagnosis in retrospect is not the answer, i. e., considering most of those patients who die as having chronic nephritis and those who recover as having "pure" nephrosis. This study suggests that the main complications are the more important practical considerations, namely, intercurrent infections which can usually be controlled and chronic progressive nephritis which cannot. It would seem that now, with better control of infections, as long as there is no evidence of progressive renal

TABLE 2.—*Results*

	Number of Cases	Normal at Time of Follow-Up	Deaths	Deaths Due to Renal Insufficiency	Follow-Up Not Conclusive
Hematuria					
++++	18	10	4	2	2
+++	1	1	..	..	..
++	0	..	..	..	..
+	1	1	..	..	..
0	9	7	2	..	..
Azotemia					
++++	4	..	2	2	..
+++	..	..	..	..	..
++	3	2	..	..	1
+	6	6	..	..	..
0	16	11	4	..	1
Hypertension					
++++	3	..	2	1	..
+++	..	..	..	..	..
++	3	3	..	..	..
+	4	4	..	..	..
0	19	12	4	1	2

insufficiency, a more favorable outlook can be entertained, no matter how many recurrences nor how long the duration or severe the other signs.

Children with the nephrotic syndrome seem to be more susceptible to infectious diseases, and their response appears to be less favorable than that of the average child. The condition of all of the children in this series seemed to be made worse by these intercurrent infections, with the exception of two children in whom measles developed.[6] Before the advent of sulfonamide and antibiotic therapy, the major cause of death in this condition was acute infection; as high as 88% of the patients with nephrosis who developed severe infectious processes died.[7] In spite of vigorous

6. In spite of the measles being of moderate severity, the nephrotic condition was favorably influenced with complete remission and no recurrence in either case. The child in Case 3 had symptoms and signs for four months, and the child in Case 21 for two years. Case 3 was reported by this department previously (Rosenblum, A. H.; Lander, H. B., and Fisher, R. M.: Measles in the Nephrotic Syndrome, J. Pediat. **35**:574-584 [Nov.] 1949).

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therapy with the then-available drugs (sulfonamide and penicillin), the primary cause of four of the six deaths in this series was acute infection. These patients all died of acute bronchopneumonia.

It appears that death due to infection may be prevented in many of the patients by vigorous sulfonamide and/or antibiotic therapy. Also some who might previously have succumbed to infection may now progress to renal failure. In this series two of the children died from renal failure, and in two others progressive renal insufficiency was developing; they were near death when this report was completed. In the future it may be that in more cases of the nephrotic syndrome the patients will die of progressive renal failure rather than infections as in the past.

This study suggests that therapy should be directed as in the past toward maintaining the physical and emotional well-being of the patient and, in addition, to the prevention and vigorous therapy of intercurrent infection.

SUMMARY AND CONCLUSIONS

Twenty-nine patients with the nephrotic syndrome were studied. Observations were made on various features of the clinical course and on the incidence of hematuria, azotemia, hypertension, and intercurrent infection. The impracticability of clinical differentiation between pure lipid nephrosis and the nephrotic syndrome or the nephrotic stage of chronic glomerulonephritis is discussed. The favorable influence of sulfonamide and antibiotic therapy of intercurrent infections on the outcome of the nephrotic syndrome is noted.

EFFECT OF HEMOPOIETIC AND OTHER AGENTS ON THE HYDROXYPHENYLURIA OF PREMATURE INFANTS

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IN THE year 1939 it was found that premature infants excreted the deaminated residues of tyrosine and phenylalanine when fed high protein diets low in vitamin C.[1] Full-term infants behaved similarly when their high-protein diets were supplemented by tyrosine or phenylalanine.[2] The administration of ascorbic acid led to consistent eradication of the hydroxyphenyluria (tyrosyluria). Liver extract decreased tyrosyluria in two of four premature infants and eliminated it in one full-term infant.

Independently, Sealock and Silberstein [3] found a similar metabolic disorder in guinea pigs fed a scorbutic diet with supplements of *l*-tyrosine. The response of this hydroxyphenyluria to the administration of ascorbic acid, an anti-pernicious-anemia preparation (liver extract),[4] or a variety of acidic substances [5] suggested that many factors contribute to complete oxidation of tyrosine and phenylalanine.

Studies of the tyrosyluria of patients with pernicious anemia [6] and of scorbutic individuals [7] have shown that the hemopoietic factors, folic (pteroylglutamic) acid

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and vitamin B_{12}, influence the metabolism of tyrosine. In vitro studies on the respiration of liver preparations with tyrosine as a substrate have confirmed these findings.[8]

Demonstration of the effect of folic acid on hydroxyphenyluria in scorbutic guinea pigs [9] led to further studies of premature infants. Similar, but not uniform, results were shown with folic acid,[10] vitamin B_{12}, and liver extract.[11] Suggestions that the effects of ascorbic acid and folic acid may be related also came from studies of experimental deficiences in the rat,[12] the monkey,[13] and the chick [14] and of megaloblastic anemia in children.[15]

The isolation of a factor necessary for the growth of Leuconostoc citrovorum 8081,[16] its close relationship to folic acid, and the augmentation of its formation from the latter by ascorbic acid [17] stimulated the study of folinic acid [18] and citrovorum factor in premature infants.

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This communication presents the results of investigation of the effects of some hemopoietic and other substances on the tyrosyluria of premature infants on high-protein diets low in ascorbic acid. It includes and extends previous studies with folic acid, vitamin B_{12} and liver extract.[19]

EXPERIMENTAL PROCEDURES

Methods, Subjects.—Thirty-five healthy premature boy babies in the Premature Center of the Colorado General Hospital ranged in age from 7 to 48 days and in weight from 1,050 to 2,980 gm. at the start of observations. Two full-term boy babies, 11 and 25 days old, were studied for periods of four and six days, respectively.

The infants took their feedings well and gained weight during the observations. Some were given antimicrobial agents because it was suspected that there was impending infection, but repeated observations revealed no changes in the tyrosyluria. General care was given by the regular nursery personnel.

Diets.—The diets consisted of dilutions of a powdered half-skimmed cow's milk preparation (alacta®) supplemented with dextri-maltose® and provided from 100 to 175 Cal. and 4 to 7 gm. of protein per kilogram per 24 hours. The daily fluid and calorie intakes averaged 150 cc. and 120 Cal. per kilogram, respectively. Attempts were made to maintain calorie and protein intakes constant over any single observation period. In addition to the basal diet, a water-miscible vitamin D_2 concentrate (calciferol [drisdol®]), or an oily preparation of vitamins A and D (percomorph liver oil) was given daily. No vitamin C was added to the diets except as part of the investigation. Foreperiods of constant diet of three or more days preceded the onset of observations.

Urine.—Urine was collected for 24-hour periods with a funnel-like tube,[20] the proximal end of which was fitted with a latex diaphragm containing an aperture 0.5 to 1.0 cm. in diameter for the penis. The diaphragm was found to prevent losses by backseepage and to maintain position more effectively in the collection tube, which led to a bottle containing 5 ml. of 6 N H_2SO_4. A metabolism mattress modified to fit the regular bassinet [21] facilitated the downward flow of urine.

The 24-hour specimens were analyzed for total hydroxyphenyl compounds (tyrosine, *p*-hydroxyphenyllactic, and *p*-hydroxyphenylpyruvic acids, expressed as tyrosine) by the method of Folin and Ciocalteau as modified by Medes [22] and adapted to the Klett-Summerson photoelectric colorimeter at a wave length of 500 mμ. In 15 infants, analysis of the urine specimen for the keto acid (*p*-hydroxyphenylpyruvic acid) was made [23] and adapted to the photoelectric colorimeter at a wave length of 450 mμ. As has been demonstrated previously,[2] keto acids accounted for approximately 15 to 35% of the total urinary hydroxyphenyl compounds. Since the response of the keto acids and total hydroxyphenyl compounds to the agents administered was similar in all cases, and since there was no correlation between the response to the different agents and the relative proportion of keto acids, the results herein reported are only in terms of total hydroxyphenyl compounds.

There were occasionally large day-to-day fluctuations in the excretion of the abnormal metabolites, possibly attributable to the difficulties in obtaining complete urine collections in a busy nursery. The significance of slight changes following the administration of an agent thus could not be evaluated. In order to minimize interpretation of the variability in the hydroxy-

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phenyluria arising from unavoided variations in protein intake, the daily excretion has been expressed as a percentage of the aromatic amino acid intake (tyrosine and phenylalanine, expressed as tyrosine).

Using analyses supplied by the manufacturer (Mead Johnson & Company), the feeding mixture of cow's milk was calculated to contain 3.96 gm. of protein per 100 ml. According to Menefee and co-workers,[24] casein accounts for approximately 80% of the protein nitrogen of cow's milk, the remaining 20% consisting of whey proteins, of which β-lactoglobulin is the largest component (55%).[25] Casein and β-lactoglobulin contain 6.1 and 5.5% tyrosine and 3.8 and 3.5% phenylalanine, respectively.[26] The aromatic amino acid content of the formula was calculated as 445 mg. (expressed as tyrosine) per 100 ml. of formula. Since all the constituents of cow's-milk protein have not been included, this represents only an approximation. It can be used validly for this study, since the feeding mixture was always of the same proportions and since the results are being interpreted qualitatively.

Supplements.—The effect of a variety of agents was studied. These included folic acid,[27] citrovorum factor,[28] folinic acid,[29] vitamin B_{12},[30] liver extract,[31] dimercaprol,[32] cortisone,[33] corticotropin,[34] methylene blue,[35] α-tocopherol,[36] *l*-glutamic acid, and *p*-aminobenzoic acid. The supplements were given singly or in combination. Ascorbic acid was given by mouth or parenterally in amounts ranging from 50 to 150 mg. daily.

No toxic reactions were noted with any of the agents in the doses employed with one exception. Pallor and rapid respirations developed in a premature infant following the administration of 5 mg. of dimercaprol intramuscularly. A hematoma developed at the site of the injection, and it is possible that some of the agent had been administered intravenously. The signs subsided rapidly, and the baby continued to do well; no additional dimercaprol was given. Irritability, large appetites, a suggestion of moonface, and slight edema developed in the infants treated with cortisone or corticotropin; these subsided readily following discontinuation of the hormones. When *l*-tyrosine was given as a supplement, it was incorporated in small portions of formula at two or more feedings. The amino acid was administered in a dose of 1.0 gm. per kilogram of body weight to two full-term infants in order to produce a significant and sustained tyrosyluria. It was also given to three premature infants in daily doses ranging from 0.9 to 3.1 gm. per kilogram of body weight over a 4- to 12-day period for total doses of 25, 26, and 22 gm. No alkaptonuria, as evidenced by darkening of the urine following alkalinization and standing for 24 to 96 hours, was found in any of these infants.

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27. Folvite,® Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

28. "Leucovorin," Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

29. Folinic acid, Eli Lilly & Company, Indianapolis.

30. Cobione,® Merck & Company, Inc., Rahway, N. J.; and rubramin,® E. R. Squibb & Sons, New York.

31. Liver extract (crude), 2 U. S. P. units (injectable) per cubic centimeter, and liver extract, 10 U. S. P. units (injectable) per cubic centimeter, Wyeth, Inc., Philadelphia.

32. Ten per cent dimercaprol (BAL) in peanut oil containing 20% benzyl benzoate, Hynson, Westcott & Dunning, Inc., Baltimore.

33. Cortone® acetate, Merck & Company, Inc., Rahway, N. J.

34. Acthar,® The Armour Laboratories, Chicago.

35. Methylene blue, 1%, intravenous solution, Intra Products Co., Denver.

36. Alpha-tocopherol acetate emulsion, Hoffmann-LaRoche, Inc., Nutley, N. J. (Preparation not available commercially).

TABLE 1.—*Effect of Folic Acid on Hydroxyphenyluria*

Subject	Birth Weight, Gm.	Age, Days	Weight, Gm.	Daily Intake		Daily Urine		
				Nitrogen, Mg./Kg.	OH-Phenyl Compounds, Mg./Kg.*	OH-Phenyl Compounds † Mg./Cc.	OH-Phenyl Compounds † Mg./Kg.	Per Cent Intake
B. L.	2,150	29	2,980	874	625	5.2	280	46
		30	2,950	885	634	5.4	357	56
		31-42	.....	Folic acid, 5 mg. p.o. daily				
		34	2,950	1020	730	4.8	368	51
		37	3,000	939	671	4.3	270	43
		41	3,100	936	670	3.4	234	35
		42-50	.....	Folic acid, 10 mg. p.o. daily				
		44	3,260	1030	737	3.1	267	36
		46	3,400	985	705	1.4	112	16
		50	3,520	955	684	0.2	17	3
A. L.	2,020	13	2,160	973	696	5.2	275	40
		14	2,160	973	696	4.1	209‡	30‡
		14-22	.....	Folic acid, 5 mg. p.o. daily				
		15	2,180	956	685	2.5	126‡	18‡
		18	2,230	935	670	1.9	94‡	14‡
		21	2,350	881	631	0.3	14	2
		22	2,500	840	601	0.4	17	3
		35	3,010	967	692	0.5	42	6
		45	3,400	984	704	0.4	29	4
R.	1,860	15-32	.....	Folic acid, 10 mg. p.o. daily				
		29	2,300	977	700	2.0	261	37
		30	2,470	910	651	1.4	173	27
		33-38	.....	Folic acid, 30 mg. I.M. daily				
		38	2,720	936	671	0.2	19	3
P.	0,970	48	2,010	1030	737	3.4	224	32
		52	2,240	801	574	3.2	187	33
		54-61	.....	Folic acid, 30 mg. p.o. daily				
		57	2,270	1002	718	4.4	227	32
		65	2,500	915	655	4.8	281	43
		74	2,780	930	666	4.1	310	47
		75-76	.....	Folic acid, 30 mg. I.M. daily				
		78	2,920	880	630	0.2	10	2
G.	1,850	17	1,800	1015	726	2.5	161	22
		18	1,850	985	705	2.6	220	31
		23-29	.....	Folic acid, 15 mg. I.M. daily				
		28	2,250	891	639	0.2	6	1
		29	2,380	805	576	0.2	4	1
O.§	1,460	37	2,380	940	674	3.2	243	34
		39	2,440	920	659	3.4	276	42
		41-43	.....	Folic acid, 30 mg. I.M. daily				
		44	2,670	916	656	2.8	247	38
		45-47	.....	Folic acid, 30 mg. I.M. daily				
		49	2,750	920	659	2.9	245	37
F. T. D.‖	3,090	11	3,380	956	685	3.6	256	37
		17	3,690	879	629	2.1	163	26
		19-24	.....	Folic acid, 30 mg. I.M. daily				
		21	3,970	1090	790	1.6	124	16
		24	4,440	980	701	0.2	10	2
F. T. L.‖	3,410	25	3,710	802	574	2.0	110	19
		27	3,860	776	556	4.1	238	43
		29	3,800	789	565	3.5	205	36
		30-43	.....	Folic acid, 20 mg. I.M. daily				
		32	3,830	781	560	1.1	51	9
		37	4,030	743	532	0.2	6	1
		43	4,180	789	565	0.2	5	1

* Tyrosine and phenylalanine expressed as tyrosine.

† Expressed as tyrosine equivalent.

‡ Urine collection incomplete; amounts calculated from estimated volume.

§ Example of lack of response found in 14 additional infants.

‖ Full-term infant who received supplement of tyrosine 1.0 gm./kg. on day prior to start of urine collections.

RESULTS

A. Effect of Various Hemopoietic Agents on Tyrosyluria of Premature Infants.—1. Effect of Folic Acid: Folic acid was administered to 20 premature infants whose ages ranged from 9 to 75 days and whose weights were from 1,600 to 3,230 gm. Nine infants received the folic acid intramuscularly, four orally, and seven by both routes. The daily dose varied from 5 to 30 mg. orally and from 15 to 30 mg. intramuscularly; the duration of administration varied from 2 to 37 days.

Five infants responded to folic acid by a marked reduction in the excretion of hydroxyphenyl derivatives (Table 1). This was achieved by the oral route of administration in two infants and by the intramuscular route in three. Two of the latter had previously failed to respond to the agent given orally.

The effect of variations in dose and route of administration on the response has been cited in a previous report.[10] For infant B. L., 5 mg. of folic acid daily by mouth for 11 days was without effect, but 10 mg. was effective in four days. For his twin, A. L., the gavage feeding of 5 mg. daily for 9 days produced a striking decrease in the excretion of abnormal metabolites by the 8th day after start of therapy, and this persisted for as long as 23 days following cessation of therapy. For infant P., the gavage feeding of 30 mg. of folic acid daily for eight days was

Table 2.—*Relation of Dose of Folic Acid to Response of Premature Infants*

	Effective		Ineffective	
	Oral	Intramuscular	Oral	Intramuscular
Mean Total Dose, Mg./Kg.	21.9	43.2	121.5	53.0
(Maximum Range)	(17.2-26.6)	(21.0-68.1)	(19.7-415.0)	(23.0-149.0)
Mean Duration of Therapy, Days	10	5	17	8
(Maximum Range)	(7-14)	(2-6)	(5-37)	(4-14)

ineffective, but the administration of the same dose intramuscularly for two days led to a prompt drop in the hydroxyphenyl excretion. For infant R., the administration of 10 mg. of folic acid orally for 18 days had little effect, but the administration of 30 mg. intramuscularly for 6 days produced a striking reduction in the tyrosyluria. Infant G. showed a similar result following administration of 15 mg. folic acid intramuscularly for seven days.

In the remaining 15 infants, folic acid was ineffective in doses ranging from 15 to 30 mg. orally for 4 to 14 days and 10 to 30 mg. intramuscularly for 5 to 37 days. The relation of the total doses employed, the route of administration, and the duration of therapy to the response of the hydroxyphenyluria is presented in Table 2.

In 10 infants in whom folic acid was ineffective, the hydroxyphenyluria subsided promptly following the administration of ascorbic acid. Two infants showed a response to the subsequent administration of vitamin B_{12}, two to liver extract, and one to folinic acid (see below).

The full-term infants, D. and L., in whom a sustained hydroxyphenyluria was successfully induced by the administration of relatively large quantities of *l*-tyrosine (supplement to diet of 1.0 gm. per kilogram of body weight), showed a prompt reduction of the excretion of tyrosyl derivatives following folic acid administration. The latter was given in dosages of 30 and 20 mg. intramuscularly for 6 and 14 days respectively, representing total doses of 43 and 41 mg. per kilogram of body weight.

TABLE 3.—*Effect of Vitamin B_{12} or Refined Liver Extract on Hydroxyphenyluria*

Subject	Birth Weight, Gm.	Age, Days	Weight, Gm.	Daily Intake: Nitrogen, Mg./Kg.	Daily Intake: OH-Phenyl Compounds, Mg./Kg.*	Daily Urine: OH-Phenyl Compounds † Mg./Cc.	Daily Urine: OH-Phenyl Compounds † Mg./Kg.	Per Cent Intake
J	1,590	29	1,950	905	649	3.4	318	49
		32	2,000	957	685	4.3	292	43
		55‡	2,820	955	684	2.7	198	28
		57-62	.....	Vitamin B_{12}, 2.5 γ I.M. daily				
		61	3,080	971	695	0.2	15	2
		62	3,080	971	695	0.2	13	2
B	1,700	20	2,130	1012	725	2.6	194	27
		22	2,270	985	705	3.8	318	45
		46‡	3,030	886	635	4.1	278	44
		50-57	.....	Vitamin B_{12}, 2.5 γ I.M. daily				
		54	3,240	925	662	0.2	11	2
		58	3,300	909	650	0.2	11	2
PII §	1,420	45	2,130	1012	725	5.4	334	46
		46	2,610	826	592	4.0	182	31
		60‡	2,500	960	688	5.0	292	42
		63-68	.....	Vitamin B_{12}, 2.5 γ I.M. daily				
		65	2,610	919	658	5.4	253	38
		68	2,720	940	674	6.0	216	32
I	1,710	24	2,290	1060	757	3.0	358	47
		25	2,290	1131	809	4.4	392	49
		30‖	2,580	1058	755	3.1	269	36
		31-38	.....	Refined liver extract, 2 units I.M. daily				
		34	2,640	1020	729	1.8	137	19
		38	2,840	1012	724	0.2	13	2
		42	2,800	1035	740	0.2	12	2
D	1,730	17	2,100	854	611	2.9	213	35
		20	2,210	880	630	4.0	214	34
		36¶	2,640	1021	730	4.2	353	48
		41	2,810	960	688	3.3	308	45
		51	3,030	985	705	3.4	315	45
		57-67	.....	Crude liver extract, 2 units I.M. daily				
		67	3,230	925	663	2.4	186	28
		68-85	.....	Refined liver extract, 2 units I.M. daily				
		74	3,570	838	600	2.8	219	37
		80	3,740	801	575	0.2	14	3
		85	3,800	906	650	1.2	11	2
K ‡	1,700	30	2,300	910	651	4.5	372	57
		32	2,380	881	631	4.5	305	48
		38‖	2,530	829	593	5.8	345	58
		39-47	.....	Refined liver extract, 2 units I.M. daily				
		44	2,660	790	566	4.5	267	47
		47	2,750	761	545	3.0	212	39

* Tyrosine and phenylalanine expressed as tyrosine.

† Expressed as tyrosine equivalent.

‡ Subject received courses of folic acid and liver extract without effect prior to vitamin B_{12}.

§ Example of lack of response found in 5 additional infants.

‖ Subject received course of folic acid without effect prior to liver extract.

¶ Subject received folic acid 22d to 85th day, *p*-aminobenzoic acid 37th to 85th day, glutamic acid 45th to 85th day.

‡ Example of lack of response found in 7 additional infants.

Sustained tyrosyluria was not produced regularly by the administration of *l*-tyrosine to a group of healthy full-term infants. The high protein-vitamin-C-deficient feeding was identical with that given to the premature infants. Apparently no vitamin C had been administered to these infants following birth. Whether the success of folic acid in suppressing a significant and sustained hydroxyphenyluria in two full-term infants consecutively represents a specific difference between full-term and premature infants remains to be investigated.

Since daily urine collections were not always made consecutively, one cannot estimate the exact time following administration of folic acid at which suppression of the tyrosyluria occurred. The consistent response of hydroxyphenyluria to ascorbic-acid administration was noted within a 24- to 48-hour period.

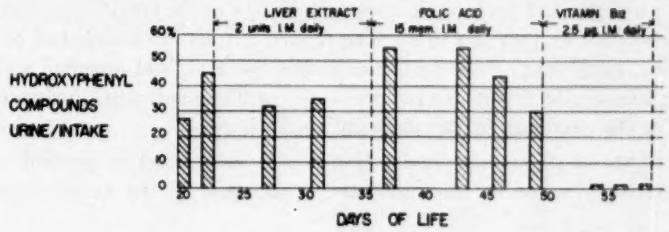


Chart 1.—Suppression of hydroxyphenyluria by vitamin B_{12} in infant B. B. (birth weight, 1,700 gm.).

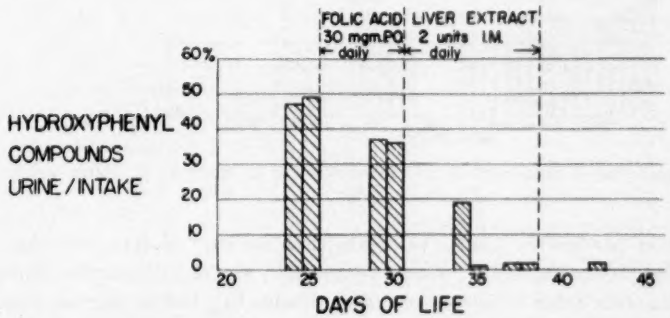


Chart 2.—Suppression of hydroxyphenyluria by liver extract in infant B. I. (birth weight, 1,710 gm.).

The suppression of the hydroxyphenyluria when it occurred following folic acid administration was as marked as that following ascorbic acid administration. The total urine hydroxyphenyl compounds fell to about one-tenth of the control-period values in both instances.

2. Effect of Vitamin B_{12}: Vitamin B_{12} was administered to eight infants with ages ranging from 29 to 63 days at the start of therapy. A daily dose of 2.5 to 5 γ intramuscularly was given for periods of 6 to 10 days.

In two infants, who had previously received liver extract and folic acid without effect, a prompt reduction in hydroxyphenyluria followed administration of vitamin B_{12} (Table 3). Both responded within five days to an average total dose of 4.1 γ per kilogram of body weight. Chart 1 illustrates the results obtained with one of these infants.

Six infants failed to respond to total doses of vitamin B_{12} ranging from 5.3 to 15.6 γ per kilogram of body weight. Three had previously had liver and folic acid. Of these infants, four subsequently responded to ascorbic acid, one to folinic acid, and one to corticotropin (see below).

3. Effect of Liver Extract: A refined liver extract was given to 10 infants 22 to 67 days of age at the start of therapy. The daily dose ranged from 2 to 10 units given intramuscularly for 7 to 14 days.

Two infants responded within 4 and 13 days with a marked reduction in the hydroxyphenyluria (Table 3). Chart 2 illustrates the results obtained in one of these infants. Folic acid had been administered prior to the liver extract with no effect. The second infant had previously received a course of crude liver extract for 11 days with a slight, and perhaps significant, reduction of the tyrosyl excretion to a level of two-thirds its previous value. The refined extract later abolished the tyrosyluria within eight days. Folic acid, *p*-aminobenzoic acid, and glutamic acid had been given serially and in combination previously to this infant without detectable alteration in the excretion of the abnormal metabolites.

Eight infants, six of whom had previously had folic acid, failed to respond to refined liver extract. In one of these subjects, a reduction in the excretion of

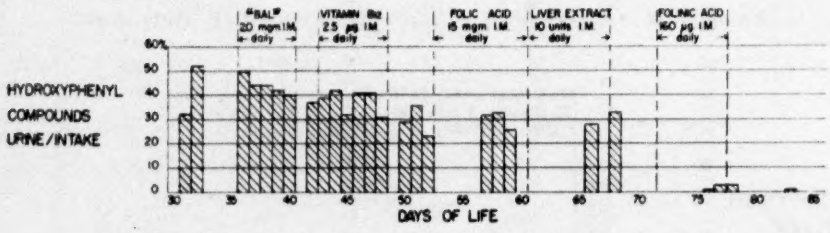


Chart 3.—Suppression of hydroxyphenyluria by folinic acid in infant B. R. (birth weight, 1,640 gm.).

"tyrosyls" to about one-half the control value was observed after 12 days of therapy. This infant subsequently showed a prompt suppression of the hydroxyphenyluria with vitamin B_{12}. One other infant responded to vitamin B_{12}, five to ascorbic acid, and one to folinic acid.

4. Effect of Folinic Acid: Seven infants ranging in age from 15 to 76 days received folinic acid in daily doses of from 160 to 3,320 γ intramuscularly over a 4- to 17-day period.

One infant responded to folinic acid after ineffective courses of dimercaprol, vitamin B_{12}, folic acid, liver extract, and cortisone. The results are illustrated in Chart 3. A total dose of 265 γ per kilogram of body weight had been given by the time the reduction in the hydroxyphenyluria was noted. This effect persisted up to seven days following the cessation of therapy, at which time observations were discontinued (Table 4). In six infants folinic acid had no effect in altering the hydroxyphenyluria. Total doses ranged from 274 to 11,550 γ per kilogram of body weight. Four infants subsequently were given vitamin C and one corticotropin with a marked reduction in the hydroxyphenyl excretion.

5. Effect of Citrovorum Factor: Citrovorum factor was administered to six infants with ages ranging from 9 to 43 days, at the start of therapy. Doses varied from 2.0×10^7 to 4.0×10^7 units intramuscularly. Total doses up to 258×10^6 units per kilogram of body weight over 7 to 24 days were ineffective.

B. Effect of Other Agents on the Hydroxyphenyluria of Premature Infants.—Miscellaneous agents, including cortisone, corticotropin, methylene blue, α-tocopherol, *l*-glutamic acid, *p*-aminobenzoic acid, and dimercaprol were administered to 13 premature infants. Because substances other than ascorbic acid had proved effective on occasion, it was decided to study the effect of two reducing substances, dimercaprol and methylene blue, and the antioxidant, α-tocopherol.

Table 4.—*Effect of Folinic Acid or Citrovorum Factor on Hydroxyphenyluria*

Subject	Birth Weight, Gm.	Age, Days	Weight, Gm.	Daily Intake		Daily Urine		
				Nitrogen, Mg./Kg.	OH-Phenyl Compounds, Mg./Kg.*	OH-Phenyl Compounds † Mg./Cc.	Mg./Kg.	Per Cent Intake
R. H.	1,640	31	2,010	989	708	4.2	231	32
		32	2,010	989	708	5.6	366	52
		40	2,220	932	667	4.2	263	40
		48	2,440	932	667	2.7	206	31
		59	2,710	932	667	2.2	173	26
		68	3,070	970	695	3.0	228	33
		72-77‡	.....	Folinic acid, 160 γ I.M. daily				
		76	3,280	913	654	0.5	9	1
		78	3,300	913	654	0.3	16	3
		83	3,410	870	623	0.2	14	1
C. §	1,360	20	1,830	1040	745	2.5	290	39
		21	1,880	1110	796	3.4	281	35
		29	2,120	981	704	3.2	225	32
		33‖	2,290	934	669	3.2	149	23
		37-40	.....	Folinic acid, 640 γ I.M. daily				
		39	2,560	970	695	3.5	247	36
		40	2,590	960	689	4.2	317	46
G. ¶	1,870	7	1,900	884	633	1.9	117	19
		8	1,930	930	666	1.9	175	26
		9-13	.....	Citrovorum factor, 20×10^6 units I.M. daily				
		13	2,020	960	687	3.3	222	32
		14-15	.....	Citrovorum factor, 40×10^6 units I.M. daily				
		14	2,050	945	677	3.4	196	29
		16	2,090	926	665	3.7	196	29

* Tyrosine and phenylalanine expressed as tyrosine.
† Expressed as tyrosine equivalent.
‡ Subject received ineffective courses of dimercaprol, vitamin B_{12}, folic acid, liver extract, and cortisone prior to trial on folinic acid (chart 3).
§ Example of lack of response found in 5 additional infants.
‖ Subject received ineffective course of folic acid prior to trial on folinic acid.
¶ Example of lack of response to citrovorum factor found in 5 additional infants.

Ten per cent dimercaprol in 20% benzyl benzoate was administered intramuscularly to eight infants starting at 12 to 36 days of age in a dose of 2.5 mg. per kilogram of body weight at six-hour intervals over a 3- to 11-day period. Daily doses ranged from 10 to 25 mg. One infant responded to the administration of dimercaprol with a marked reduction in the excretion of hydroxyphenyl compounds three days following the start of therapy. The total dose given was 31 mg. per kilogram of body weight. Seven days following the final therapy, at which time observations were discontinued, the tyrosyluria persisted at the same low level (Table 5 and Chart 4). In the remaining seven infants, the hydroxyphenyluria was not signifi-

cantly altered by dimercaprol in doses ranging from 24 to 146 mg. per kilogram of body weight. There was a prompt subsequent response to ascorbic acid in four infants and to folinic acid in one.

Fifty milligrams of α-tocopherol acetate was given orally three times a day for six days to two infants without effect upon the tyrosyluria. Similarly, 1.5 mg.

TABLE 5.—*Effect of Miscellaneous Agents on Hydroxyphenyluria*

Subject	Birth Weight, Gm.	Age, Days	Weight, Gm.	Daily Intake		Daily Urine		
				Nitrogen, Mg./Kg.	OH-Phenyl Compounds, Mg./Kg.*	OH-Phenyl Compounds † Mg./Cc.	OH-Phenyl Compounds † Mg./Kg.	Per Cent Intake
S.....	1,900	10	1,830	950	681	4.1	228	33
		11	1,800	935	670	3.0	210	31
		12-14	.....	Dimercaprol, 5.0 mg. I.M. q. 6 hr. daily				
		14	1,930	900	645	2.6	175	27
		15	1,950	892	639	0.7	51	8
		18	2,040	975	699	0.3	18	3
		21	2,220	895	641	0.2	17	3
Z.‡.....	1,750	19	1,950	970	690	3.1	265	39
		21	1,990	1000	716	4.3	274	38
		22-27	.....	Dimercaprol, 2.5 mg. I.M. q. 6 hr. daily				
		27	2,150	925	663	2.8	205	31
		28	2,200	925	663	3.2	312	47
		28-32	.....	Dimercaprol, 5.0 mg. I.M. q. 6 hr. daily				
		34	2,400	931	667	3.9	291	44
		35	2,400	931	667	2.8	345	52
N.....	1,360	34	1,590	1060	759	3.9	250	33
		35	1,600	1055	755	3.2	219	29
		57-66	.....	Cortisone acetate, 25 mg. I.M. daily				
		58§	2,230	1000	716	7.7	285	40
		66	2,580	1082	776	4.6	371	48
		67	2,680	1042	747	5.2	296	40
		81‖	3,200	1050	752	4.6	248	33
		82-86	.....	Corticotropin, 37.5 mg. I.M. daily				
		84	3,410	984	705	0.9	63	9
		85	3,420	980	703	0.2	11	2
		86	3,450	973	697	0.2	14	2
		95	3,690	1060	760	0.1	10	1
T.¶.....	1,280	19	1,550	890	638	4.0	181	28
		20	1,570	880	630	3.5	125	20
		27	1,770	895	641	4.1	272	42
		35	2,020	885	634	4.1	231	37
		42-49	.....	Corticotropin, 20 mg. I.M. daily				
		42	2,120	965	688	5.0	450	65
		43	2,130	960	691	4.4	213	31
		44	2,140	1060	759	3.9	308	41
		45	2,150	1125	805	3.9	237	30
		48	2,180	1110	795	3.4	312	39
		49	2,180	1110	795	0.3	18	2

* Tyrosine and phenylalanine expressed as tyrosine.
† Expressed as tyrosine equivalent.
‡ Example of lack of response found in 6 additional infants.
§ Example of lack of response found in 2 additional infants.
‖ Subject received folinic acid from day 76 to day 80.
¶ Subject received dimercaprol and vitamin B_{12} prior to corticotropin.

of methylene blue given intramuscularly daily for six days failed to alter the hydroxyphenyluria in two infants.

Because of the general metabolic effects of corticotropin and cortisone, it seemed worth studying the effects of these hormones on tyrosyluria. Three infants were receiving therapy because of retrolental fibroplasia.

One infant in the present series received a five-day course of corticotropin intramuscularly, totaling 188 mg. A marked reduction of the tyrosyluria was evident after four days. At that time the infant had received a dose of 46 mg. per kilogram of body weight. Prior courses of cortisone and folinic acid had been ineffective. The results are illustrated in Chart 5. Another infant received a total of 150 mg. (70 mg. per kilogram of body weight) of corticotropin in eight days. A marked reduction of tyrosyluria occurred suddenly on the eighth day of therapy.

Three infants received cortisone for 10 to 14 days, the doses totaling 250 to 350 mg. No significant alteration of the hydroxyphenyluria was noted.

The nonspecific action of a variety of unrelated acidic substances in reducing the hydroxyphenyluria of scorbutic guinea pigs has been demonstrated by Sealock.[5]

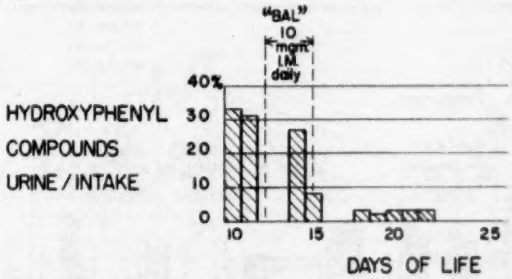


Chart 4.—Suppression of hydroxyphenyluria by dimercaprol (BAL) in infant B. S. (birth weight, 1,900 gm.).

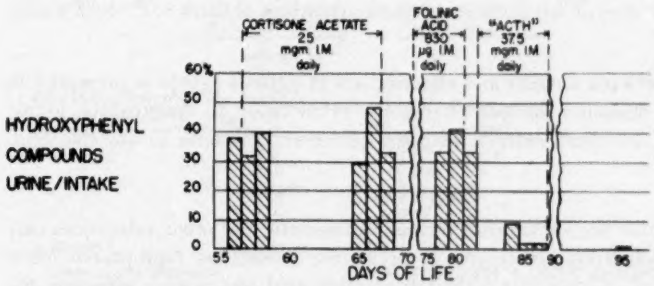


Chart 5.—Suppression of hydroxyphenyluria by corticotropin (ACTH) in infant B. N. (birth weight, 1,360 gm.).

It appeared that the effect of these substances was closely related to, or dependent upon, the ascorbic acid present in the tissues of the animal and the ability of acids to mobilize these tissue reserves. Glutamic acid, one of these substances, was administered to two premature infants. Totals of 780 and 1,020 mg. were given orally over 13 and 14 days, respectively, with no alteration of the tyrosyluria. Para-aminobenzoic acid (60 mg. orally per day) was also given to these infants for 21 and 28 days. No significant change in the tyrosyluria was found. One of these infants responded subsequently to refined liver extract and the other to ascorbic acid. It is interesting, in view of its structural similarity to the aromatic amino acids, that no increase in the hydroxyphenyluria was noted during the administration of *p*-aminobenzoic acid.

TABLE 6.—*Relation of Dose of Agent to Response of Hydroxyphenyluria of Premature Infants*

Agent	Effective		Ineffective	
	Total Dose Administered	Duration of Therapy, Days	Total Dose Administered	Duration of Therapy, Days
Vitamin B_{12}	4.1 γ/kg.	5	7.9 γ/kg. (5.3-15.6)	7 (6-10)
Liver Extract	4.1 units/kg.	6	10.3 units/kg. (5.4-21.5)	9.4 (7-14)
Folinic Acid	265 γ/kg.	5	3,260 γ/kg. (274-11,550)	9 (5-17)
Citrovorum Factor	.....	..	141.8×10^6 units/kg. (85.8×10^6-258.0×10^6)	10.5 (7-24)
Dimercaprol	31.2 mg./kg.	3	63.4 mg./kg. (23.7-146.0)	5.6 (3-11)
Corticotropin	57.8 mg./kg.	6	.....	..
Cortisone	.....	..	115.5 mg./kg.	12
Methylene Blue	.....	..	4.8 mg./kg.	5.5
α-Tocopherol	.....	..	408 mg./kg.	6
Glutamic Acid	.....	..	287 mg./kg.	15
p-Aminobenzoic Acid	.....	..	498 mg./kg.	24.5

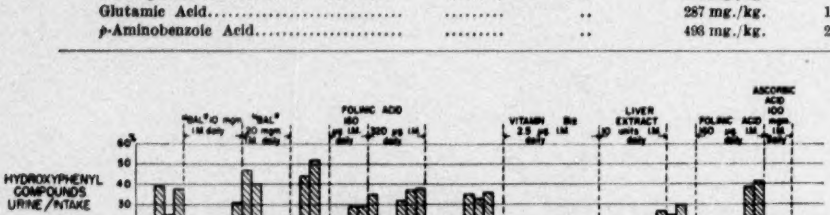


Chart 6.—Lack of effect of various agents on hydroxyphenyluria in infant B. Z. (birth weight, 1,750 gm.).

The relation between amount and effectiveness of various agents is presented in Table 6. Chart 6 describes the lack of response of an infant to dimercaprol, folinic acid, vitamin B_{12}, and liver extract, with the customary response to ascorbic acid.

COMMENT

This investigation has shown that various hemopoietic and other substances may eradicate the spontaneous tyrosyluria of premature infants on high-protein diets devoid of vitamin C (Table 7). Although ascorbic acid was always effective, the

TABLE 7.—*Response of Hydroxyphenyluria of Premature Infants to Various Agents*

Agent	Subjects Tested	No. Successes
Folic Acid	20	5
Folinic Acid	7	1
Citrovorum Factor	6	0
Vitamin B_{12}	8	2
Liver Extract	10	2
Dimercaprol	8	1
Corticotropin	2	2
Cortisone	3	0
α-Tocopherol	2	0
Methylene Blue	2	0
Glutamic Acid	2	0
p-Aminobenzoic Acid	2	0

other effective agents, with the exception of corticotropin, were inconsistent in their action. The suppression of the tyrosyluria was not governed by dose, duration, or order of therapy with these factors, and their mode of action remains obscure.

The present incomplete knowledge of the intermediary metabolism of the aromatic amino acids, as modified from Peters and Van Slyke,[37] is presented in Chart 7. Much of the information has been gleaned from studies of diseases associated with excretion of intermediary metabolites, but additional work with isotopically labeled phenylalanine and tyrosine has confirmed this general scheme.[38] It has been demonstrated in recent studies utilizing extracts of rat liver homogenates that the obligate step to the oxidative degradation of tyrosine is transamination,[39]

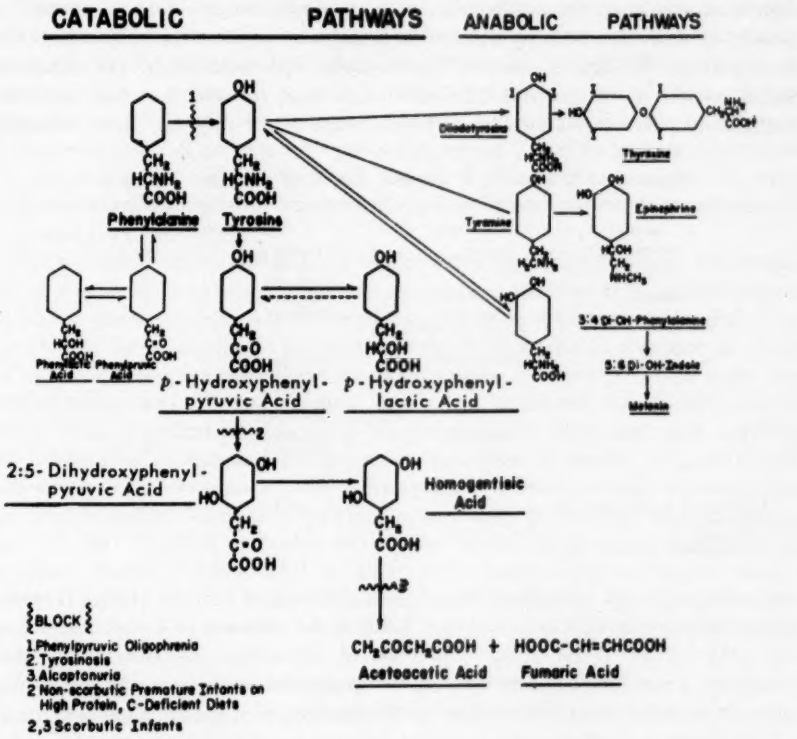


Chart 7.—Metabolism of phenylalanine and tyrosine (modified from Peters and Van Slyke [37]).

37. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry Interpretations, Ed. 2, Baltimore, Williams & Wilkins Company, 1946, Vol. 1.

38. Moss, A. R., and Schoenheimer, R.: The Conversion of Phenylalanine to Tyrosine in Normal Rats, J. Biol. Chem. **135**:415, 1940. Schepartz, B., and Gurin, S.: Intermediary Metabolism of Phenylalanine Labeled with C^{14}, Federation Proc. **8**:248, 1949. Weinhouse, S., and Millington, R.: Ketone Body Formation from Tyrosine, J. Biol. Chem. **181**:645, 1949. Lerner, A. B.: On the Metabolism of Phenylalanine and Tyrosine, ibid. **181**:281, 1949.

39. (*a*) Schepartz, B.: Transamination as a Step in Tyrosine Metabolism, J. Biol. Chem. **193**:293, 1951. (*b*) Knox, W. E., and LeMay-Knox, M.: The Oxidation in Liver of L-Tyrosine to Acetoacetate Through p-Hydroxyphenylpyruvate and Homogentisic Acid, Biochem. J. **49**: 686, 1951.

with α-ketoglutarate as the amino acceptor. Pyridoxal phosphate has been shown to act as a coenzyme in this reaction, whereas ascorbic acid is required for the complete oxidation of the deaminated residue, *p*-hydroxyphenylpyruvate.

The existence of a complex interrelationship between the metabolism of tyrosine, ascorbic acid, and various hemopoietic factors has been indicated by studies in patients with blood dyscrasias and ascorbic acid deficiencies, and in animals with folic acid and ascorbic acid deficiencies. A summary of evidence from the literature is presented in Table 8.

Because of the similarity of the alteration of tyrosine metabolism in folic acid- and ascorbic acid-deficiency states, as well as the overlapping efficiency of these agents in restoring the metabolism of the aromatic amino acids to normal, the possibility arose that both participated in a single metabolic step, in tyrosine oxidation, perhaps through a common intermediate. The isolation of the citrovorum factor, as well as the probably identical folinic acid, revealed that folic acid has a biologically active derivative 8 to 100 times more potent than the parent substance,

TABLE 8.—*Effectiveness of Various Agents in Reducing Tyrosyluria*

Animal	Deficiency	Dietary Supplements		
Guinea Pig *	Scurvy	Ascorbic acid	+	
		Liver extract	+	−
		Folic acid	+	
Monkey †	Ascorbic acid and folic acid (megaloblastic anemia)	Ascorbic acid	+	
		Folic acid		−
Humans	Pernicious anemia ‡	Liver extract	+	
		Desiccated hog stomach	+	
		B_{12}	+	
		Ascorbic acid		−
.....	Scurvy §	Ascorbic acid	+	
		Folic acid	+	−
		B_{12}		−

* Footnotes 3, 4, 9b, and 58.
† Footnote 42.
‡ Footnote 6.
§ Footnotes 7 and 54.

depending upon the method of assay.[40] The efficiency of in vitro biological systems in converting folic acid to citrovorum factor in the presence of ascorbic acid [17] and the enhancement of the urinary excretion of citrovorum factor by the scorbutic individual given folic acid and vitamin C [41] suggested that citrovorum factor might play a role as the active intermediate in the metabolism of the aromatic amino acids.

However, the efficacy of vitamin C in eradicating the induced hydroxyphenyluria of the monkey with megaloblastic anemia while under the influence of "aminopterin" (4-aminopteroylglutamic acid), at which time the synthesis of citrovorum factor was blocked, argued against this hypothesis.[42] Furthermore, folinic

40. Footnote 18. Shive, W.; Bardós, T. J.; Bond, T. J., and Rogers, L. L.: Synthetic Members of the Folinic Acid Group, J. Am. Chem. Soc. **72**:2817, 1950.

41. Burchenal, J. H.: Folic Acid and Its Interrelationship with Ascorbic Acid in the Megaloblastic Anemia of Infancy, Personal Communication, in Lederle Laboratories Bulletin, February 1951, p. 45.

42. Salmon, R. J., and May, C. D.: Metabolism of Tyrosine in Experimental Megaloblastic Anemia and in Scurvy in the Monkey, J. Lab. & Clin. Med. **36**:591, 1950.

acid failed to eradicate the induced tyrosyluria in the monkey with megaloblastic anemia.[43] The lack of effect of folinic acid on the hydroxyphenyluria of the premature infant substantiates this finding.

Whether or not the action of folic acid or other hemopoietic factors depends on tissue levels of vitamin C remains unknown. Studies correlating the white-cell and plasma ascorbic acid contents with the efficacy of these agents in suppressing the tyrosyluria of premature infants may be illuminating. If the effect of these agents is the result of an intermediate formed through interaction with ascorbic acid, it appears that citrovorum factor is not the active substance.

There is some evidence to suggest that folic acid and ascorbic acid act independently at different stages in the metabolism of tyrosine and phenylalanine. In scorbutic infants [7] and guinea pigs [9b] given folic acid, the appearance of homogentisic acid in the urine following the administration of tyrosine was frequently unassociated with any significant hydroxyphenyluria. This suggested that the production of homogentisic acid proceeded in these instances through a pathway which was not influenced by folic acid. The failure of ascorbic acid to diminish the spontaneous hydroxyphenyluria of patients with pernicious anemia [6a] and its prompt suppression following the use of liver extract and vitamin B_{12} [6b] points to an action of these agents in the utilization of the deaminated residues of tyrosine which is independent of ascorbic acid.

The possibility arises, therefore, of an alternative metabolic pathway. The oxidation of *p*-hydroxyphenylpyruvic and *p*-hydroxyphenyllactic acids is usually carried out by an enzyme system in which ascorbic acid is an essential component. It is possible that these deaminated residues may also be degraded by a system in which one or more of the hemopoietic factors is necessary. One can postulate under the latter circumstances a "chain reaction" similar to the scheme for the synthesis of nucleic acids, described by Vilter and his co-workers.[44] Here folic acid, together with other unknown substances, activates the formation of purines and pyrimidines from amino acids. Vitamin B_{12} carries the process to the formation of nucleosides from purines and pyrimidines. Other factors may carry the reaction through further stages to the formation of nucleic acids. The variable response of persons with pernicious anemia to folic acid,[44] of infants with megaloblastic anemia to vitamin B_{12} [45] and of animals with experimental macrocytic anemia to liver extract [46] may be conditioned by the presence or availability of some other critical factor or factors in this "chain reaction."

Whether the inconsistent response of the hydroxyphenyluria of premature infants to these agents can be explained in a similar fashion remains to be determined. What is presupposed is a reaction in which some unknown substance or a

43. Salmon, R. J., and May, C. D.: The Effect of Folinic Acid (Citrovorum Factor) and of Cortisone on the Metabolism of Tyrosine in the Scorbutic Monkey, Arch. Biochem. **32**:220, 1951.

44. Vilter, R. W., and others: Studies on the Relationships of Vitamin B_{12}, Folic Acid, Thymine, Uracil, and Methyl Group Donors in Persons with Pernicious Anemia and Related Megaloblastic Anemias, Blood **5**:695, 1950.

45. Woodruff, C. W.; Ripy, H. W.; Peterson, J. C., and Darby, W. J.: Variable Response to Vitamin B_{12} of Megaloblastic Anemia of Infancy, Pediatrics **4**:723, 1949.

46. Heinle, R. W., and others: Effect of Extrinsic Factor, Liver Extract, and Folic Acid on Induced Macrocytic Anemia of Swine, J. Lab. & Clin. Med. **32**:1398, 1947. Cartwright, G. E.; Tatting, B. S.; Ashenbrucker, H., and Wintrobe, M. M.: Experimental Production of a Nutritional Macrocytic Anemia in Swine, Blood **4**:301, 1949.

series of substances needs to be present, the absence of which results in hydroxyphenyluria. Lack of knowledge about this hypothetical substance or substances is indicated by the failure to suppress hydroxyphenyluria even when the hemopoietic factors were administered consecutively and in doses much larger than those which on other occasions had been effective (Chart 6).

Whether or not the action of ascorbic acid in tyrosine metabolism is due to its oxidation-reduction potential has remained unsettled. The isomer of vitamin C, *d*-isoascorbic acid, while equally potent as a reducing agent, has a minimal effect on the hydroxyphenyluria of premature infants.[2] Likewise, *d*-isoascorbic acid when administered to the scorbutic guinea pig with high doses of *l*-tyrosine, is not as efficient as *l*-ascorbic acid in accelerating the disappearance of the deaminated residues from the urine.[47] However, recent in vitro studies, using guinea-pig-liver suspensions [48] and extracts of rat-liver homogenates [50b] have shown that the disappearance of *l*-tyrosine or its deaminated residues from the reaction mixture was accelerated by the addition of *d*-glucoascorbic acid and isoascorbic acid, respectively. The rate of disappearance was similar to that noted following the addition of *l*-ascorbic acid. Since *d*-glucoascorbic acid is not retained by the tissues of the intact animal, but is excreted rapidly in the urine, the inefficacy of this and related isomers of *l*-ascorbic acid in altering the in vivo metabolism of tyrosine may thus be explained.[48] The reducing substance, dimercaprol, was tried in eight premature infants, but with only one success, and the antioxidant α-tocopherol was ineffective in two infants even when given in large doses. It is interesting to note that the same in vitro studies with extracts of rat-liver homogenates which demonstrated the effect of ascorbic and isoascorbic acids on *p*-hydroxyphenylpyruvate oxidation revealed the ineffectiveness of compounds with similar reducing or oxidizing properties (glutathione and peroxide) or a similar reductone structure (dihydroxymaleic acid).[50b]

The effect of corticotropin and some adrenocortical steroids on the metabolism of tyrosine and phenylalanine in premature infants has recently been reported.[49] The tyrosyluria on an ascorbic acid-deficient-high-protein diet was consistently suppressed by corticotropin and inconsistently by cortisone. Desoxycorticosterone, dehydrocorticosterone, progesterone, testosterone, and compound "L" of Reichstein (*allo*pregnane-3(β) : 17(β) : diol-20-one) were ineffective. Although adrenocortical stimulation leads to depletion of the gland's ascorbic acid,[50] the effect of corticotropin in these infants apparently did not involve the utilization of stored ascorbic acid. Study of the serum and white-blood-cell ascorbic acid was reported as

47. Sealock, R. R., and Silberstein, H. E.: The Excretion of Homogentisic Acid and Other Tyrosine Metabolites by the Vitamin C-Deficient Guinea Pig, J. Biol. Chem. **135**:251, 1940.

48. Painter, H. A., and Zilva, S. S.: The Influence of L-Ascorbic Acid on the Disappearance of the Phenolic Group of L-Tyrosine in the Presence of Guinea Pig-Liver Suspensions, Biochem. J. **46**:542, 1950.

49. Levine, S. Z.; Barnett, H. L.; Bierman, C. W., and McNamara, H.: Effect of ACTH and Some Adrenocortical Steroids on the Metabolism of Tyrosine and Phenylalanine in Premature Infants, Science **113**:311, 1951.

50. Sayers, G.; Sayers, M. A.; Liang, T. Y., and Long, C. N. H.: The Cholesterol and Ascorbic Acid Content of the Adrenal, Liver, Brain, and Plasma Following Hemorrhage, Endocrinology **37**:96, 1945.

showing no changes during corticotropin therapy, and, since the infants were on high protein-vitamin-C-deficient diets, one would not expect them to have had considerable stores of vitamin C.

It has been demonstrated that relatively large amounts of dehydroisoandrosterone can replace folic acid as a growth factor for some micro-organisms.[51] Recent studies with cortisone have demonstrated that this steroid can similarly replace folic acid and citrovorum factor as growth factors for Streptococcus faecalis and Leuconostoc citrovorum.[52] Although 10,000 times more cortisone than citrovorum factor was required by L. citrovorum, the steroid was 20 times more potent for this organism than folic acid. Moreover, cortisone reversed the inhibitory effect of "aminopterin" on the growth of these organisms. The comparatively small changes in the growth of one organism induced by cortisone suggested that it was probably a catalyst rather than an end-product of the enzyme reaction inhibited by "aminopterin." In vitro studies with liver homogenates from folic acid-deficient, as well as nondeficient, rats revealed that cortisone stimulates the oxidation of added tyrosine in amounts considerably greater than those reported for folic acid.[8a] These data suggest that cortisone, and perhaps other adrenocortical steroids, affects the metabolism of tyrosine via a pathway the nature of which is as obscure as the one proposed for the various hemopoietic factors.

It has been pointed out that folic acid and related substances, as well as ascorbic acid, may be responsible for the rupture of the aromatic nucleus and consequently for the production of nonphenolic residues.[7] Some have argued that the dependence of the complete degradation of high doses of *l*-tyrosine on the presence of *l*-ascorbic acid or one or more of the hemopoietic factors does not necessarily imply a connection between the normal function of these substances and the normal metabolism of the aromatic amino acids.[53] For example, scorbutic individuals under usual dietary conditions do not excrete abnormal quantities of hydroxyphenyl compounds.[54] Furthermore, the premature infant does not manifest the defect on diets providing less than approximately 4.0 gm. of protein per kilogram of body weight per day, though these may apparently be nutritionally adequate. Although phenylalanine is an essential amino acid, premature and scorbutic infants show no marked stunting of growth or malnutrition which one might expect if the aromatic amino acids were not utilized. Finally, following the ingestion of tyrosine by scorbutic and premature infants, a considerable quantity of the consumed amino acid cannot be accounted for by the urinary hydroxyphenyl output.[55] These observations lend

51. Gaines, D. S., and Totter, J. R.: Pteroylglutamic Acid-Like Effect of Dehydroisoandrosterone on Growth of Certain Microorganisms, Proc. Soc. Exper. Biol. & Med. **74**:558, 1950.

52. Gaines, D. S.; Broquist, H. P., and Williams, W. L.: Certain Relationships Between Pteroylglutamic Acid, Citrovorum Factor, and Cortisone, Proc. Soc. Exper. Biol. & Med. **77**:247, 1951.

53. Painter, H. A., and Zilva, S. S.: The Influence of l-Ascorbic Acid on the Rupture of the Benzene Ring of l-Tyrosine Consumed in High Doses by Guinea-Pigs, Biochem. J. **41**:511, 1947.

54. Rogers, W. F., and Gardner, F. H.: Tyrosine Metabolism in Human Scurvy, J. Lab. & Clin. Med. **34**:1491, 1949. Woodruff, C. W.: Tyrosine Metabolism in Infantile Scurvy, ibid. **36**:640, 1950.

55. Morris, Harpur, and Goldbloom.[7] Knox and LeMay-Knox.[89b]

credence to the hypothesis that the usual pathways of tyrosine metabolism may not be dependent on the function of ascorbic acid or the hemopoietic factors. Nevertheless, the specific nature of the biochemical defect in premature infants and scorbutic individuals with hydroxyphenyluria remains a matter of interest. The effect of hemopoietic factors on tyrosine and phenylalanine metabolism, the disturbance of the metabolism of these amino acids in individuals with pernicious anemia or scurvy and in nonscorbutic premature infants, and the occurrence of an anemia as yet unexplained in premature infants lead to the speculation that some phenolic derivative may participate in the red blood cell developmental processes.

SUMMARY AND CONCLUSIONS

Studies have been made of the effect of various hemopoietic and other factors on the hydroxyphenyluria of 35 nonscorbutic premature infants fed high protein-vitamin-C-deficient diets. Using almost complete abolition of hydroxyphenyluria as an index, folic acid was found effective 5 times in 20 trials, folinic acid 1 in 7, citrovorum factor 0 in 6, vitamin B_{12} 2 in 8, and liver extract 2 in 10. Dimercaprol was effective in 1 in 8 trials, but methylene blue and α-tocopherol were ineffective twice each. Corticotropin was effective in each of two and cortisone ineffective in each of three trials. Ascorbic acid was always effective.

It is suggested that when ascorbic acid is absent from the diet of premature infants, another metabolic pathway may be called upon for degradation of the deaminated residues of tyrosine and phenylalanine. This hypothetical alternative may represent a "chain reaction" requiring for completion a factor or series of factors, of which the presence of all or the absence of any one may be responsible, respectively, for the positive or negative results obtained when the hemopoietic agents were used.

Correspondence

PHYSIOLOGICAL AVAILABILITY OF VITAMIN A FROM CAPSULES

To the Editor:—We would like to bring to the attention of your readers certain inconsistencies and inaccuracies in the article "Physiological Availability of Vitamin A from Capsules" by A. E. Sobel and A. A. Rosenberg appearing in the November issue.

The article draws a comparison between the serum vitamin A levels in adults fed large numbers of three different capsules and a reference oil of vitamins A and D. One of the products studied was our preparation "vi-aqua," identified as product "C."

In attempting to explain wide differences in vitamin A absorption claimed by the investigators, they attribute the differences to variations in the disintegration time required for the three different capsules. Here their data appear to be completely erroneous.

The authors claim that in a pepsin solution, capsule C ("vi-aqua") did not disintegrate for *four hours,* while the other two capsules in the study disintegrated in a matter of 8 to 50 seconds. As all three capsules are made of gelatin—and as repeated tests in our laboratories have demonstrated that the "vi-aqua" capsule will disintegrate in such a solution within two to five minutes, their data are obviously incorrect.

Equally perplexing is the authors' observation that our capsule ("vi-aqua") disintegrated rapidly in an aqueous solution whereas one of the other capsules failed to disintegrate in from *four to five hours.* Again, considering that both capsules are made of gelatin, and our own tests showing they both dissolve in approximately the same time, there appears no explanation for these differences.

Further confusion arises from the chart (p. 614) which shows disintegration time in *seconds,* while the authors in their discussion speak of the relative disintegration times of the different capsules in *hours.* There is a complete lack of correlation between the two different time measurements.

Another inconsistency appears in Chart 1 which depicts the rise in serum vitamin A concentrations after the administration of the test dose. This chart clearly shows that product C ("vi-aqua") produced the second highest rise in serum vitamin A concentration (only slightly less than that produced by product A). Yet in the following chart (Chart 2) product C ("vi-aqua") is shown to produce the lowest increase in serum vitamin A concentration. As these two sets of figures do not coincide, it is obvious that at least one chart is in complete error.

Another puzzling aspect is that capsule A and capsule C are both made under the same process of converting the normally lipo-soluble vitamin A into water-soluble form. This process was developed in the research laboratories of the U. S. Vitamin Corporation in 1943, and is now protected by U. S. patent 2,417,299.

As the manufacturer of capsule A is licensed under this patent, and further as the authors found each of the capsules to contain the potencies of vitamin A as claimed on the label, we can see no explanation or justification for the discrepancies in the vitamin A blood concentrations claimed to be found by the investigators when these two capsules were given to the same patients.

Serum vitamin A tests with "vi-aqua" capsules in our laboratories and by others (unpublished data) show that absorption of vitamin A from these capsules compares with that from our aqueous products ("vi-syneral" vitamin drops and "aquasol" vitamin A). The relative comparison of vitamin A absorption and availability from these products with oily solutions and emulsions is well known, having been reported in various published articles and best described in the following two publications:

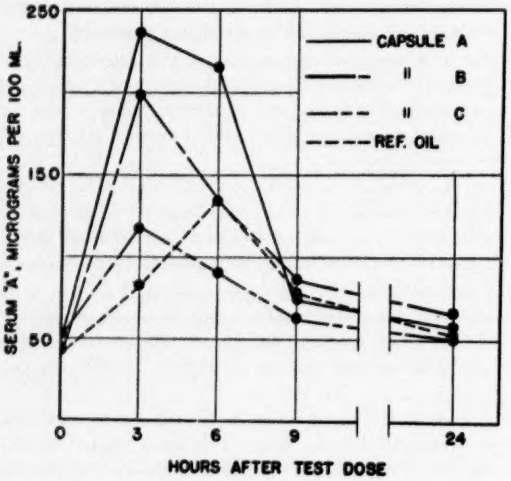
Lewis, J. M.; Bodansky, O.; Birmingham, J., and Cohlan, S. Q.: Comparative Absorption, Excretion, and Storage of Oily and Aqueous Preparations of Vitamin A, *J. Pediat.* **31**:496-508 (Nov.) 1947.

Lewis, J. M., and Cohlan, S. Q.: Comparative Absorption of Various Types of Vitamin A Preparations, *M. Clin. North America* **34**:413-424 (March) 1950.

W. C. MARTIN, M.D.
Medical Director, U. S. Vitamin Corporation

To the Editor: —We appreciate your thoughfulness in permitting us to see the comments of Dr. W. C. Martin, Medical Director of U. S. Vitamin Corporation on our article "Physiological Availability of Vitamin A from Capsules," which appeared in the A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN **84**:609, (Nov.) 1952.

The appearance of our article has already brought realization to our hope "that this study will stimulate others to test the physiological availability of vitamin A from the numerous preparations on the market." A medical director of a major pharmaceutical house, whose product was not examined, has written as follows:



Mean changes in serum vitamin A following the administration of capsules A, B, C, and reference oil.

"I am wondering if you could make available to me four reprints of your recent article entitled "Physiological Availability of Vitamin A from Capsules," which appeared in the November issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

"I think this article is very well done and feel that we should follow some such procedure in formulating vitamin capsules. I should like the extra copies for distribution amongst our company here.

"Thank you very much."

Many of Dr. Martin's comments do not bear analysis. We confine ourselves to the most pertinent. Dr. Martin claims that our article attempts to explain the wide differences in the absorption of vitamin A by differences in the disintegration time of the capsules studied. Dr. Martin has apparently overlooked our comments on pages 614 and 615, namely:

"The above tests (disintegration time) simply serve to emphasize the point made by Oser, that *disintegration studies, physical appearance, or analytical values are not reliable indices of physiological availability.*" (Parentheses and italics not in original.)
and

"Disintegration studies and the state of dispersion provided no clear indication of the physiological availability of the three capsules tested."

Several typographical errors, which were not caught in proofreading, appear in the article. In Table 3, the word "seconds" should read "minutes." Charts 1 and 2 were derived from the mean values, following Case 8 in Table 2. In Chart 1, the graph lines are correct, but "B" and "C" in the legend should be interchanged. A revised chart accompanies this note. This, we hope, resolves the burden of Dr. Martin's comments on disintegration time and absorption.

Dr. Martin's comments on the patent held by his company have no bearing on the subject of the article. Our energies were directed to a problem of interest to the physician rather than to patent rights. We repeated the experiments with pepsin and water, questioned by Dr. Martin, and found that the differences stated exist, contrary to the assertion of Dr. Martin. It is well known that the properties of gelatin vary depending on the source, mode of preparation, and subsequent treatment.

Absorption from aqueous dispersions does not predict absorption from a capsule, as indicated in these studies. Even aqueous dispersions vary with respect to improved absorption. For example, we reported previously that the ratio of dispersing agent to vitamin A influences the absorption of vitamin A (Kramer, B.; Sobel, A. E., and Gottfried, S.: Am. J. Dis. Child. **73**:543-553, 1947; Sobel, A. E.; Besman, L., and Kramer, B.: ibid. **77**:576-591, 1949; Sobel, A. E.: Vitamins and Hormones **10**:53, 1952.). A liquid containing 20% dispersing agent results in higher levels than one containing 11% dispersing agent. Lewis and co-workers have observed that particle size has an influence on the absorption of vitamin A (*Pediatrics* **5**:425, 1950).

If our paper has encouraged the kind of approach we have proposed in evaluating pharmaceutical vitamin preparations, we shall feel that our efforts have been worthwhile. We would redirect Dr. Martin's attention to the factors which we postulate as having possible bearing on physiological availability. These appear on page 614, and not one includes disintegration studies. They are as follows:

1. The site at which the capsule releases its contents.
2. The stability of vitamin A in the gastrointestinal contents.
3. The state of dispersion of vitamin A released to the gastrointestinal contents.

Our study was a first attempt to answer some of the questions raised by the physician and students of human nutrition, the most important of which, as indicated earlier by Oser and later by us, is the physiological availability of the capsule contents.

Albert Edward Sobel, Ph.D.,
Head, Department of Biochemistry, The Jewish Hospital of Brooklyn
Abraham Rosenberg, M. S.,
Research Chemist

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

Conversion of Glucose to Amino Acids by Brain and Liver of the New-Born Mouse. R. J. Winzler, K. Moldave, M. E. Rafelson Jr. and H. E. Pearson, J. Biol. Chem. **199**:485, 1952.

The incorporation in vitro of radioactive carbon from uniformly labeled C^{14}-glucose into the individual protein-bound amino acids of adult mouse brain and of one-day-old mouse brain or liver has been compared with the incorporation in vivo of glucose into the protein-bound amino acids of one-day-old mouse brain, liver, or intestine. The metabolic behavior of one-day-old mouse brain, especially in the in vitro incubations, was found to be unique in that all the essential and nonessential amino acids except proline and threonine were significantly labeled. Radioactivity in the other systems was largely limited to aspartic acid, glutamic acid, alanine, serine, and glycine (aminoacetic acid). The data are indicative that in the one-day-old mouse brain degradation products of amino acids may be in metabolic equilibrium with intermediates derived from glucose. This could result in appearance of radioactive carbon from glucose in essential amino acids with no net synthesis of these amino acids. The results are, therefore, not necessarily at variance with the well-established concept of essential amino acids, but do emphasize the caution necessary in transferring interpretation from in vitro to in vivo experiments.

Page, Cleveland [A. M. A. Arch. Neurol. & Psychiat.].

Incorporation of Labeled Methionine into Protein by Pituitary Tissue. J. B. Melchior and M. N. Halikis, J. Biol. Chem. **199**:773, 1952.

Measurements were made of the ability of pituitary tissue to incorporate a labeled amino acid into protein in vitro. The method described permits measurements with the single rat pituitary. Pituitary tissue was found to be much more active in the incorporation of the labeled amino acid than was liver. The activity was significantly greater in young animals. After the first two weeks of life the activity remained relatively constant, with a tendency to decrease in the older rats. No significant difference was found during the phases of the estrous cycle or during pregnancy. The male gland had the same activity per gram as the gland of the normal adult female; because of the smaller size of the animal, the total activity in the male was significantly less than that in the female. During lactation a significant decrease in the ability of the gland to label protein was observed.

Page, Cleveland [A. M. A. Arch. Neurol. & Psychiat.].

Effects of Large Loads of Electrolytes. J. L. Gamble, W. McL. Wallace, L. Eliel, M. A. Holliday, Margaret Cushman, Janet Appleton, Anita Shenberg, and Jean Piotti, Pediatrics **7**:305 (March) 1951.

The effect of a large intake of various sodium and potassium salts on the retention of electrolytes and on the distribution of water in the body was studied in normal growing infants. Renal adjustment to elevation of intake was found to take place slowly, with the result that very large retentions of the electrolytes added to the food developed over the eight-day periods of study. It was also found that an increased retention of sodium was accompanied by a reduction of potassium retention, and the reverse effect was observed when potassium salts were given. When sodium bicarbonate was used, a large part of the retained sodium was transferred to the intracellular compartment, whereas potassium chloride caused a removal of intracellular sodium. These shifts of sodium prevented change in the plasma bicarbonate in the presence of widely different retentions of sodium and chloride. The results of these studies may be interpreted in terms of the fluid and electrolyte therapy of dehydration as indicating the hazard of overhydration if treatment is continued after replacement of the body fluid losses. They also imply that excessive use of solutions of sodium chloride or sodium bicarbonate may further increase an existing deficit of potassium.

From the Authors' Summary.

PLASMA AND ERYTHROCYTE CHEMISTRY OF THE NORMAL INFANT. R. R. OVERMAN, J. N. ETTELDORF, ANNE C. BASS, and G. B. HORN, Pediatrics **7**:565 (April) 1951.

One hundred eighty-eight normal infants from birth to 2 years of age have been studied in a serial manner with regard to concentrations of Na, K, and Cl in plasma and erythrocytes; plasma Ca, nonprotein nitrogen, protein and CO_2; plasma pH and venous hematocrit values. These values have been compared with those of normal women at term and with other adult normal values. Nineteen samples of blood from the umbilical artery were likewise analyzed for comparison

Serial and progressive alterations in the measured variables occurred, and in several regards the normal chemistry of infant body fluid departs sharply from normal adult values.

FROM THE AUTHORS' SUMMARY.

TISSUE RESPIRATION AND BODY SIZE. L. VON BERTALANFFY and W. J. PIROZYNSKI, Science **113**:599 (May 25) 1951.

It is well known that in many mammalian species there is a systematic decrease of metabolic rate per unit of weight with increasing size. In order to investigate the possibility that this phenomenon is due to alterations in tissue metabolism during growth, the authors measured oxygen uptakes of several tissues in the albino rat, using animals of varying weights. They found a slight decrease in the average oxygen-consumption values in liver, heart, and diaphragm with increasing body size, but no significant differences for the other tissues examined. As the result of these experiments the authors conclude that the decrease of basal metabolic rates with increasing size is not due to cellular factors, but must be sought for in factors residing in the organism as a whole.

FORBES, Dallas, Texas.

USE OF POTASSIUM GLUCONATE IN HYPOPOTASSEMIA. ADOLPH BERHARD, Science **113**:751 (June 29) 1951.

In view of the fact that in certain patients for whom potassium therapy is indicated the chloride ion is undesirable, the author suggests that potassium gluconate be substituted for the more commonly used potassium chloride. This material can be autoclaved and administered either orally or parenterally. One gram of potassium gluconate is equivalent to 160 mg. or 4.2 mEq. of potassium. The author reports that potassium gluconate has been used for several months with excellent results and no evidences of toxicity.

FORBES, Dallas, Texas.

ACTION OF AN ANTIRETICULAR CYTOTOXIC SERUM IN IMMATURE AND DYSTROPHIC INFANTS. G. BROGI and VERPOTTI, Clin. pediat. **34**:1 (Jan.) 1952.

Bogomolets, a Ukrainian scientist, has prepared and worked with an antireticular cytotoxic serum from rabbits, goats, and horses which had received injections of an extract of human organs (spleen and bone marrow) rich in reticular histiocytic tissue. A similarly prepared serum was used in the present study in the hope that it would prove to be a stimulant to the metabolic and growth processes of the immature or dystrophic infant. Seventeen immature infants and 6 dystrophic infants were given injections of this serum every four days for four to six weeks in increasing amounts. Each of the 23 infants began immediately to show a gain in weight of about 50 gm. a day, whereas previously their weights had been stationary. Many biochemical and hematological data were collected in this study.

HIGGINS, Boston.

RIBOFLAVIN AND CARBOHYDRATE METABOLISM. SEVERINO PEDONE, Riv. clin. pediat. **49**:251 (April) 1951.

The author brings to our attention the fact that riboflavin in a 1 mg. dose has an inconstant action, depending on the subject's neurovegetative constitution; in a 2 mg. dose it has a constantly and modestly hyperglycemic action, even in those cases in which with a 1 mg. dose a slight hypoglycemic action was apparent. Moreover it has a certain potentiating effect on the hyperglycemic activity both of glucose and of epinephrine; it has a moderating action on hypoglycemia from insulin. When riboflavin is associated with desoxycorticosterone it has a hyperglycemic

action; when associated with desoxycorticosterone and insulin it has a more moderating effect than the one obtained with riboflavin plus insulin. Through the experiments carried out and the results obtained the author holds to the hypothesis that riboflavin may have an action similar to that produced by epinephrine; presumably stimulating the vegetative sympathetic nervous centers through the action of the adrenal cortex, riboflavin is transformed from provitamin into vitamin.

FROM THE AUTHOR'S SUMMARY.

DIETETIC TREATMENT OF OBESITY IN CHILDREN. L. HOSTOMSKA, M. STRAKOVA, J. BLUDSKY, and J. DEDIC, Pediat. listy **4**:204, 1951.

A reduced diet for children used in the children's clinic is described. Only 50 to 60% of the caloric need is covered by this diet. The reduction is at the expense of carbohydrate and fats, which are allowed at a weight proportion of 4:1 or 3:1. A sufficient amount of animal protein (2 gm. per kilogram of weight daily) is secured, as well as sufficient vitamins (A, B, and C). For practical purposes a plan for such reduced diets for children from 6 to 15 years of age is added, and the experiences of the authors in hospital and outpatient treatment are described.

FROM THE AUTHORS' SUMMARY.

PLASMA BY MOUTH IN THE TREATMENT OF DYSTROPHIC INFANTS. P. SEVCIK, Pediat. listy **7**:103, 1952.

The giving of plasma by mouth diluted with equal amounts of 5% dextrose solution is useful in the treatment of dystrophic infants and in cases in which there is a diminished tolerance for the foods usually given. This method, of course, does not replace intravenous administration of plasma for rehydration, i. e., in the first 24 to 48 hours.

FROM THE AUTHOR'S SUMMARY.

HYPOCALCEMIA IN INFANCY. H. C. CHAO, Chinese M. J. **67**:229 (April) 1951.

H. C. Chao discusses postacidotic hypocalcemia and hypocalcemia of the newborn. Briefly, the infant with dehydration and acidosis has lost extracellular water and electrolytes, chiefly Na, Cl, and HCO_3. To maintain osmotic balance, intracellular water with electrolytes (chiefly K and P) moves into the extracellular spaces. The state of acidosis facilitates mobilization of Ca and P from bones. Thus intracellular water and electrolyte are also depleted. When the infant is treated with intravenous fluid and electrolytes, acidosis is rapidly corrected. Indeed, the correcting processes may overshoot the mark, throwing the pH and bicarbonate above normal. The body then, by natural hemostasis, regains its balance after swinging back and forth several times.

Meantime, the cells, hungry for their lost electrolytes, reclaim them. K goes back to the cells; Ca and P to the bones. Phosphatase is needed for this phase. Serum values of Ca, P, K, and phosphatase are therefore all temporarily low during the postacidotic period. It is at this time that symptoms of hypocalcemia may occur with neuromuscular excitability, labored respirations, bradycardia, abdominal distention, pallor, sometimes edema, and a hemorrhagic tendency. Treatment is prompt administration of calcium.

Hypocalcemia is more apt to occur in the newborn for several reasons. The calcium equilibrium in the neonate is quite labile, and there is a tendency for the calcium to be lower and the phosphorus higher than in the older person. It is believed that the parathyroids may be physiologically insufficient at this age, thus accounting for some of this instability. The immaturity of the kidneys, by retaining P, may depress serum calcium levels. Maternal osteomalacia, prevalent in China, may induce fetal rickets. Mild alkalosis may induce tetany by reducing the amount of ionized calcium.

Whatever the cause, newborn infants do sometimes show symptoms of tetany from a few hours to a few weeks after birth. Edema, vomiting, hemorrhagic manifestations, and neuromuscular excitability are the symptoms and vary with the intensity of the hypocalcemia. Treatment may be given with calcium gluconate, intravenously in acute cases, or calcium chloride, orally when possible. Dihydrotachysterol can be used as an adjuvant.

MACDONALD, Pittsburgh.

Vitamins; Avitaminoses

RICKETS IN CORREZE. DEPAILLAT, Presse méd. **58**:796 (July 8) 1950.

A study of rickets was established in the Department of Correze (in South-Central France) by the Academy of Medicine, primarily to determine the necessity for adding vitamins to evaporated milk. In this underprivileged district, 25 to 40% of the babies have rickets, and rachitic deformities are carried over into adult life in great number.

The poor mineralization of the soil in the high areas accounts for some of the lack of calcium, while old habits of dress and failure to expose the babies to sunshine can explain the lack of vitamin D. Very few babies are breast-fed and most of the older infants are on a diet of milk exclusively.

Solution of this problem will depend not only on addition of minerals and vitamins to the milk but also on education of the population in matters of diet and hygiene.

DAFFINEE, Melrose, Mass.

Hygiene; Growth and Nutrition; Public Health

THE ASTORIA PLAN: A DECADE OF PROGRESS. HAROLD JACOBZINER, J. Pediat. **38**:221 (Feb.) 1951.

Jacobziner reviews the progress of school health services in New York City, with particular reference to the evolution of such services from the Astoria Health Demonstration Study. This study was started in 1936; in 1941, the Astoria Plan, as it had become known, was started throughout the entire city of New York.

This plan concentrates school health services on children most in need of care. It has also evolved the concept that physician, nurse, teacher, and parent must act as a coordinated team for the best interests of the individual child. This perspective has improved the school health services to a point where they may be viewed with pardonable pride. Now is the time to look forward to further progress. The coordinated team may be tightened by sharpening the perspective of the physician, nurse, teacher, and parent and by increasing the emphasis on preventive pediatrics.

MACDONALD, Pittsburgh.

THE OVERLOADED CURRICULUM IN SECONDARY EDUCATION. C. SAIZ DE LOS TERREROS, Acta pediat. españ. **8**:397 (April) 1950.

In a very sprightly manner, Dr. de los Terreros criticizes the overloaded curriculum in secondary schools, both parochial and secular, as a menace to a child's physical and mental health.

The hours described by the author are incredible: 8:30 a. m. to 6:30 p. m. with time out only for a noon meal and with no break in studies for recreation. Boarding schools are no better. There is insufficient rest and too many subjects to be mastered.

There must be an understanding between the teaching profession and the medical profession, especially the pediatricians who act as school physicians.

Three types of improvement are essential, (1) simplification of material to be studied, (2) diminution of work hours, and (3) more physical education.

The author mentions the work of Maria Kaezynska, Vaclar Prioda, Agatha Bowly, and others, and quotes the São Paulo, Brazil, congress on school hygiene, 1941, in the statement "There cannot exist good mental health if all of our psychic functions are in a bad state of equilibrium." A reappraisal of the curriculum in the secondary schools might diminish mental illnesses.

The doctor says that no one doubts that the curriculum can be stretched even as rubber, or a balloon, but that there is a limit, and asks what good the balloon or rubber band is when it has been stretched to its limit.

ALLEN, San Francisco.

CRANIAL DEVELOPMENT IN THE INFANT. ALVAREZ MORUJO, Acta pediat. españ. 8:787 (July) 1950.

Dr. Morujo, who is professor of anatomy at the University of Salamanca, states that many studies of the infant skull in comparison with that of the adult were made and that many comparisons were made of various diameters.

Many authors have discussed the various shocks to which the infant's head is subjected and the way in which the infant's skull is adapted to such shocks.

The author, however, is primarily interested in the large variety of shapes and sizes of individual bones in the skulls of infants of the same age. The article shows pictures of a wide variety of different shapes found in the occiput, the temporal, and the sphenoid bones. The greatest variety of all is noted in the ethmoid bones, which are largely cartilaginous.

Dr. Morujo describes various centers of ossification within the bones and states that within a given bone the rate of growth may be unequal in these centers. He discusses the relation between the growth of the maxilla and the mandible, and the start of dentition and mastication. He also discusses the formation of the various bone sinuses.

The size and shape of the fontanels and the suture lines play a part in the mechanics of skull growth and development.

He concludes that the major number of variations occur in the bones at the base of the cranium, and that the fontanels and sutures contribute to differences. The position of these sutures and fontanels are related to the cranial mechanics at birth as well as during the growth of the child.

The growth within the dome of the cranium comes earlier than that of the mandibular bones, and the rate of growth is greater.

ALLEN, San Francisco.

SCHOOL EXAMINATION STATISTICS. FERNANDO CIRAJAS, Acta pediat. españ. 9:572 (May) 1951.

The state of Valladalid has a long history of school examinations dating back to 1928. The author examines the statistics and presents the statistics since 1943 graphically.

These studies show that the number of children examined yearly since 1943 has been fairly constant. Some of the results are as follows: Tuberculin-positive reactions have increased. Immunizations to smallpox and diphtheria have increased steadily and rapidly. These became compulsory in all national schools in 1950-1951. X-ray examinations have been increased to include all children of school age. Psychological examinations and, where needed, psychiatric studies have been increased in number. Cooperation between school physicians and the nurses from the Provincial Health Service has been responsible for the great reduction of pediculosis among the children. Dental caries is still widespread, although tending to follow a downward curve. Hearing defects are on the increase. Cardiac lesions are diminishing. Among other defects which are on the downward trend are hypertrophy of the tonsils, dermatoses, and anomalies of the vertebral column and eye defects.

The author states that (1) more education on sanitation and hygiene and better psychological methods in teaching, and (2) increase in number of doctors and nurses with reorganization of School Medical Services, are especially necessary now.

ALLEN, San Francisco.

IMPORTANCE AND USE OF VITAL STATISTICS IN HEALTH PROGRAMS. CHARLES G. BENNETT, Bol. Soc. Boliviana pediat. 4:17 (March) 1950.

The author, an international consultant of the U. S. Public Health Service, lent to the Department of Health in Bolivia, discusses his subject under the following divisions: mortality, birth certificates, communicable disease reporting, and the relation of this type of information to a more economic use of money for proposed health programs.

He also discusses the use of hospital statistics, especially the patient cost per day. The daily average patient load would indicate the need for new hospitals in certain regions.

The average stay in the hospital would indicate whether or not some are kept too long, and whether, as is often the case with infantile diarrheas, the babies had been hospitalized too late to prevent deaths.

Statistics can be used to construct a basis for health work by demonstrating what the problem is and where it is. It is an excellent way to appraise programs and serves as propaganda for securing adequate funds to carry out needed programs.

ALLEN, San Francisco.

ANALYSIS OF THE CAUSES OF INFANT MORTALITY. J. BLECHA, Pediat. listy **7**:79, 1952.

An analysis of the causes of infant mortality is made. The material used was the report of the State Statistical Office (Bohemia and Moravia), on the one hand, and replies to a questionnaire sent to 30 of the largest children's departments and maternity units in Bohemia, on the other. The first method was used to compare the years 1947, 1948 and 1949 and the second to analyze the relations in the years 1949 and 1940. Thirty-four thousand infants in maternity units and 25,000 children admitted to children's departments were included in replies to the questionnaire. The statistical report shows the importance of early age, prematurity, and respiratory infections.

The questionnaire concentrated on the group of newborn infants both mature and premature, and on the first and second age groups (from the 2d to the 5th month of life and from the 6th to the 12th, respectively). Forty-one and two-tenths per cent of infants who die in the first year of life die in the first 28 days; the percentage in the first age group is 39.4 and in the second age group 19.4%. The death rate is highest in March and lowest in September.

Premature infants comprise 7.3% of total births. In mature children the commonest cause of death is infection, mainly respiratory and intestinal. Atrophy and dystrophy are evaluated. Fatal atrophy was marked in the first age group (30.6—37.2%); in the second age group it was much lower (11.3—16.7%). Repeated infection was a commoner cause of dystrophy than other causes (nutrition and rickets). The mortality in breast-fed infants is about half that in wholly or partially artificially fed. Breast-fed infants comprised 15% of admissions in the first age group, and in the second age group the children admitted were exclusively or partially artificially fed.

The main diseases in infancy are respiratory infections, the toxic syndrome, noninfectious enterocolitis (dysentery syndrome), congenital defects, and staphyloderma. These diseases comprise 75 to 80% of all admissions and cause 66 to 75% of the mortality.

FROM THE AUTHOR'S SUMMARY.

Prematurity and Congenital Deformities

SUCCESSFUL SURGICAL SEPARATION OF SIAMESE TWINS. PIERO E. CARRAI, Riv. clin. pediat. **50**:265 (April) 1952.

The author describes a successful separation of Siamese twins. An urgent operation was necessary because one of the two sisters died soon after birth. The surviving sister is still, after five years, in good health and shows normal development.

FROM THE AUTHOR'S SUMMARY.

Acute Contagious Diseases

INEFFECTIVENESS OF AUREOMYCIN IN PREVENTING THE PRIMARY VACCINIA REACTION. ROBERT H. HIGH and CHARLES B. REINER, J. Pediat. **38**:60 (Jan.) 1951.

Aureomycin affects certain Rickettsia and large viruses. Perhaps, thought High and Reiner, it might be active against the virus of vaccinia. If it were, it would be useful in the management of eczema vaccinatum and of secondary vaccination. They gave aureomycin in doses of 50 mg. per kilogram to a group of vaccinated infants and compared the effect on the primary vaccinia reaction with a group of controls. Aureomycin, in this dose, does not affect the evolution of the primary vaccinia reaction.

MACDONALD, Pittsburgh.

PROBLEM OF EMBROPATHY FROM RUBELLA. GIAN TONDURY, Bull. Schweiz. Akad. med. Wissensch. **7**:307 (July) 1951.

Since the first observations of lesions in infants whose mothers had acquired rubella at the beginning of the pregnancy, numerous other cases have been reported which tend to show that, among the 46 varieties described, lesions of the crystalline lens and of the organ of Corti and cardiac malformations are most frequent. According to Bourquin's statistics, based on 146 observations, the cases of congenital cataract were seen with a maximum frequency when the mother was ill during the fourth and fifth week of pregnancy. When the illness was later,

the cases were rare, and disappeared entirely after the 12th week. The critical period for the formation of a congenital cataract coincides with the first processes of differentiation of the embryonic crystalline lens. A few figures will illustrate the development of the crystalline lens.

At the end of the fourth week and the beginning of the fifth week (28th to 30th day), the crystalline plate appears in the epidermis which covers the ocular vesicle. Between the 30th and the 35th day, the crystalline vesicle becomes isolated, and at the end of the sixth week (40th to 42d day), the first crystalline fibers begin to differentiate.

The youngest embryo, of 21 mm., showed disorders of the lens of the first degree. The disposition of the lens was normal, but the fibers during differentiation showed a vacuolar deformation. Judging by the examination of embryos of a more advanced stage, this deformation would lead to complete destruction with the formation of a central cataract. An embryo of 64 mm. had a similar central disorder of the lens, and in addition it could be seen that this destructive process had reached the fibers of the lens which are formed secondarily. This same degeneration of the lens fibers, which spreads out peripherally, has been ascertained in a fetus of 32 cm. and also in a newborn infant. In spite of the same anamnesia, an embryo of 140 mm. showed a peripheral cataract, while the nucleus of the lens was more or less intact. In all the embryos, these disorders of the lens were accompanied by a remarkable delay in the growth of the eye.

FROM THE AUTHOR'S SUMMARY.

ELECTROCARDIOGRAM IN THE ACUTE PHASE OF POLIOMYELITIS. L. SALMI and M. MALOSSI, Clin. Pediat. **34**:17 (Jan.) 1952.

Electrocardiograms were taken for 62 patients in the acute stage of poliomyelitis. Three patients showed extrasystoles, 1 a heart block, and 11 neurovegetative dystonia. These findings confirm the belief that the poliomyelitis virus may cause myocarditis.

HIGGINS, Boston.

POLIOMYELITIS: EPIDEMIOLOGY, PROPHYLAXIS AND TREATMENT. JUAN L. MORALES, Acta pediat. españ. **8**:1142 (Oct.) 1950.

Dr. Morales discusses the epidemiology of poliomyelitis with special reference to the health conditions, water sewage disposal, open markets, etc., in Seville and the surrounding country.

He speaks of the need for lay, medical, and nursing education regarding the recognition and diagnosis of this disease compared with other similar condition. He believes that the use of convalescent serum and the closing of schools during an epidemic might not help the epidemic but might dispel some of the hysteria. (Schools should not be closed if theaters, swimming pools, etc., are allowed to stay open.)

During an epidemic there should be no tonsillectomies, tooth extraction, or oral surgery; it is best not to do mass smallpox vaccinations at this time.

Dr. Morales believes that there must be hospitals or centers like the one in Buenos Aires, Argentina, or Warm Springs, Ga., for physical therapy. There should be orthopedic surgeons, nurses, and therapists to treat all the sequelae of poliomyelitis. From the moment of recovery from the acute stage, the correct orthopedic positions and postures should be maintained to prevent worse deformities. Early hospitalization is imperative, and the doctor quotes Dr. Lewin on the need for a firm bed in transporting patients, "Better the floor of a Ford than the soft cushions of a Rolls Royce."

There is, of course, no immunizing procedure, but parents can be taught not to give unboiled water and milk and raw fruit and vegetables during an epidemic. Hands should be washed with a brush and soap, which is far superior to antiseptic or so-called antiseptic solutions.

During epidemics, children should not travel, should not be allowed to become fatigued or chilled, and should not be allowed to run around in wet clothing or to expose themselves to the sun excessively.

The author believes that sick children and carriers should be isolated four to six weeks—not just during the incubation period but until all evidence of virus infection of the throat has disappeared.

The duty of the medical profession and health department should include the founding of organizations for the aid of families who have children with poliomyelitis as well as such obvious things as better reporting and better hospital facilities.

The public should be educated to fight flies and should be instructed in the use of powdered calcium hypochlorite for use in the feces, and in the washing of diapers; also in the rural areas they should be instructed in the proper chlorination of drinking water.

ALLEN, San Francisco.

DIPHTHERIA IMMUNIZATION BY THE USE OF DIPHTHERIA TOXOID. Y. RAMON, Acta pediat. españ. **9**:390 (April) 1951.

Dr. Ramon, who is an honorary director of the Pasteur Institute in Paris, gives the history of the development of immunization in diphtheria from antitoxin and toxin-antitoxin to toxoids with their degree of protection, chemical and physical composition, etc.

After the 1931 meeting in London of the League of Nations Committee on Social Hygiene, large numbers of countries began a more widespread use of the toxoid products either by compulsion or by education. The author discusses the results collected from reports from various localities including Europe, America, South America, Japan, Turkey, Russia, and Yugoslavia. More detailed figures as to mortality and morbidity rates are given with regard to the United Kingdom and the United States of America.

The author says that many young physicians in America have never seen a case of diphtheria in the course of either their training or their practice. He believes that more widespread use of reports of cases and deaths and better reports might well give the same results in all countries.

ALLEN, San Francisco.

Chronic Infectious Diseases

SPINAL BLOCK IN TUBERCULOUS MENINGITIS UNDER TREATMENT WITH STREPTOMYCIN P. NICOLAI, Clin. pediat. **34**:38 (Jan.) 1952.

Blockage of the spinal fluid flow in tuberculous meningitis may occur in untreated patients, in patients receiving inadequate streptomycin therapy, in patients in whom there has been tissue irritation due to streptomycin, and in patients having an allergic reaction in the meninges to the drug. Treatment was easier and the prognosis better in the cases of the first, third, and fourth types listed above; patients receiving inadequate streptomycin therapy usually died.

HIGGINS, Boston.

SULFONE ALONE AND ASSOCIATION WITH STREPTOMYCIN AND VITAMINS IN THE TREATMENT OF EXPERIMENTAL MILIARY PULMONARY TUBERCULOSIS IN RABBITS. SEVERINO PEDONE and ORESTE BRUNO BARTOLI, Riv. clin. pediat. **50**:245 (April) 1952.

The authors have experimentally analyzed the influence of (*a*) sulfone, (*b*) sulfone combined with streptomycin, and (*c*) sulfone combined with streptomycin and vitamin A, on the evolution of miliary pulmonary tuberculosis of the rabbit.

Sulfone by itself has a certain therapeutic efficacy by transforming miliary pulmonary tuberculosis of the rabbit (which proved to be rapidly mortal for control animals) into a disease with slow course and with a tendency to becoming chronic.

Sulfone combined with streptomycin has caused clinical recovery. In the animals killed after a certain time the lesions showed a tendency to healing. In previous experiments carried out by the authors good results were obtained in the treatment of experimental miliary pulmonary tuberculosis of the rabbit with streptomycin alone, but with the above-mentioned combination results have been more rapid. The association of sulfone with streptomycin and vitamin A has given still more satisfactory results. The association of these three medicaments suggested by Cocchi for human beings has, therefore, proved to be the therapy giving best results in the treatment of miliary pulmonary tuberculosis of the rabbit.

FROM THE AUTHORS' SUMMARY.

LATE RESULTS OF ATELECTASIS OF THE LUNGS IN TUBERCULOSIS OF CHILDHOOD. R. NEUMANN, Pediat. listy **7**:97, 1952.

The late results of atelectasis of the lungs in tuberculosis of childhood are described. The consolidation and induration lead to deformity of the wall of the affected bronchus with resulting

bronchiectasis. In the upper lobes the entire lobe is usually affected or at least two segments. Since these changes are irreversible operation should be undertaken to remove the affected parts. To the present time lobectomy has been successfully performed in 2 patients.

FROM THE AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

FRAGILITY OF RED BLOOD CELLS FROM NEWBORN INFANTS AND CHILDREN WITH CYANOTIC CONGENITAL HEART DISEASE. FORREST H. ADAMS and SHIRLEY C. CUNNINGHAM, J. Pediat. **39**:180 (Aug.) 1951.

The blood from children with cyanotic congenital heart disease showed only slightly greater fragility than the normal. Oxygenation of the blood had little or no effect on fragility. The authors were unable to confirm the increased fragility of fetal blood reported by others. Red blood cell fragilities were determined with a spectrophotometer. MACDONALD, Pittsburgh.

ACUTE INFECTIOUS LYMPHOCYTOSIS. U. PELLEGRINI, Lattante **22**:577 (Oct.) 1951.

The blood pictures of 2 children with acute infectious lymphocytosis were studied over a period of one month, by which time the blood counts had returned to normal. The symptoms of one child, 9 months old, were fever, loss of appetite, restlessness, and a slight moist cough, and the symptoms of the other child, 7 years old, were fever, general malaise, abdominal pain, and diarrhea. The children were at no time critically ill and recovered clinically in two weeks. The spleen was not enlarged, nor was there any marked lymph node enlargement in either case. In the acute phase, there were about 30,000 white blood cells, with 80% lymphocytes. There were 24% and 37% lymphocytes in the bone marrow cells, whereas the normal finding is about 9%; this figure is to be expected from the increase in blood lymphocytes. No other cytological, physical, or chemical abnormalities in the blood were detected. Acute infectious lymphocytosis is apparently a clinical entity, characterized by a stimulation of the lymphocyte production.

HIGGINS, Boston.

PERSISTENCE OF THE COMMON ARTERIAL TRUNK. S. LO BIANCO, Lattante **22**:666 (Nov.) 1951.

A 6-week-old infant with congenital malformations of the heart died of malnutrition. Autopsy examination revealed a very small left auricle, but hypertrophy of the right auricle and the ventricles. There was an open foramen ovale, and atresia of the auricular and ventricular septa. The pulmonary veins were very small. The pulmonary artery and the aorta emerged as a common trunk from the left ventricle. The pulmonary circulation was taken care of wholly by five large bronchial arteries, one to each lobe of the lungs, branching off from the aorta just below the left subclavian artery.

HIGGINS, Boston.

ENCEPHALOFACIAL NEUROANGIOMATOSIS. P. BRUSA and L. PARENZAN, Minerva pediat. **4**:65 (Feb.) 1952.

The case of a 10-year-old girl with the Sturge-Weber syndrome is reported and discussed. She had a hemangioma over the right side of the face, glaucoma of the right eye, a history of convulsive movements of the right arm, attacks of petit mal and episodes of severe headaches. The right side of the head was larger than the left. Spinal fluid was normal. Electroencephalograms revealed abnormalities in the right occipital area and a dysrrhythmia typical of epilepsy.

HIGGINS, Boston.

Diseases of Nose, Throat, and Ear

EOSINOPHILIC GRANULOMA. MARSHAK, Harefuah **43**:173 (Dec.) 1952.

A 5-year-old boy was admitted to a hospital Jan. 8, 1952. Six weeks before admission he began to complain of pain in the region of the bridge of his nose. A short time afterward a swelling appeared in this region and remained about a week. It reappeared after four weeks.

At the same time a swelling was noted in the region of the vertex of the skull, near the region of the anterior fontanel. The general condition of the child was good; there was no febrile rise. Upon his admission a small swelling was found near the bridge of the nose. The edges of the swelling were not well delimited. A defect in the bone could be felt in the center of the swelling. Another swelling was found in the region of the anterior fontanel; it was a little larger. Roentgenograms showed defects in the skull bones, about 2 cm. in diameter, in the region of swelling. No bony defects were found in other parts of the skeleton. The blood cell count showed 2.3% eosinophiles. Operation, on Jan. 17, 1952, showed an eosinophilic granuloma at each site; the destruction of bone in the region of the anterior fontanel extended to the dura. Histologic study of the curetted bone was reported as revealing an eosinophilic granuloma. Some histiocytes were noted, in addition to the eosinophilic polymorphonuclear leucocytes. Both these lesions disappeared with x-ray therapy. On March 4 a swelling and bone defect were noted in the region of the left mastoid. This bone defect cleared up completely with x-ray therapy alone. Follow-up examination seven months after the child was first seen showed complete recovery. Since Jaffe and Lichtenstein described this lesion in 1940, there has been considerable difference of opinion as to whether it is a distinct clinical entity or whether it is related to Hand-Chrstian-Schüller disease or Letterer-Siwe disease. The author does not express his own opinion.

SAVITSKY, New York [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Diseases of Lungs, Pleura and Mediastinum

BRONCHOPNEUMONIA DUE TO ASPIRATION OF AN ANTIDIARRHEIC MIXTURE. MAHAIM, Schweiz. med. Wchnschr. **82**:615 (June 7) 1952.

Vegetable elements added to milk can accidentally cause catastrophe. A detailed history is given of an infant who, from the age of one month, had persistent diarrhea, and so an antidiarrheic mixture rich in pectin and cellulose was added to the milk. When about 3½ months old the little girl was admitted to the hospital. Bronchial embarrassment and bronchopneumonia developed with severe attacks of dyspnea. She died at the age of 5 months. At postmortem examination chronic bronchopneumonia was found in both lower lobes with purulent bronchiolectases, due to foreign bodies which proved to be vegetable debris.

AMBERG, Rochester, Minn.

Diseases of the Gastrointestinal Tract, Liver, and Peritoneum

CONSTRUCTION OF A RECTAL SPHINCTER AND RESTORATION OF ANAL CONTINENCE BY TRANSPLANTING THE GRACILIS MUSCLE. KENNETH L. PICKRELL, T. RAY BROADBENT, FRANK W. MASTERS, and JAMES T. METZGER, Ann. Surg. **135**:853 (June) 1952.

This paper presents a new principle in anal reconstructive surgery: the transplantation of the gracilis muscle to construct an anal sphincter. The technic of the operation is given in detail. The procedure has been used successfully on four children who had been classed as incurable or hopelessly beyond the realm of reconstruction because of neurological lesions affecting the nerve supply of the perineum.

BANTIN, Omaha.

TREATMENT OF CONGENITAL INGUINAL HERNIA. J. W. DUCKETT, Ann. Surg. **135**:879 (June) 1952.

Treatment of inguinal hernia in childhood or infancy is strictly surgical. Operative treatment, based on the simple principle of removing the hernial sac, is necessary for cure of congenital inguinal hernia. There should be little morbidity, no mortality, and no recurrences.

With few exceptions, operation should be done at whatever age diagnosis is made. Application of a truss to retain a hernia is justified only when operative treatment must be postponed for some good reason.

A survey of 380 operations is made. Complications and associated anomalies are discussed.

BANTIN, Omaha.

THIRTY YEARS' EXPERIENCE IN THE TREATMENT OF VOMITING IN INFANCY ACCORDING TO THE TEACHINGS OF PAVLOV. B. EPSTEIN, Pediat. listy **7**:82, 1952.

The author considers it a suitable time, now that the teachings of Pavlov have at last received their deserved recognition, to draw attention to his own previous works from the years 1922, 1927, and 1936, in which he elaborated a new conception of the pathogenesis of vomiting in infancy based on the teachings of Pavlov. The conception arose from the physiological observation that peristaltic function (the constriction reflex) is lacking in infants, which explains the "physiological" tendency to vomit in healthy young infants. Gastric peristalsis develops and the tendency to vomit is lost only when solid food is given. Therefore, vomiting may occur in infants from the most diverse causes. The repetition of these external stimuli (exteroceptive impulses) leads to the development of a pathological conditioned reflex. In this way the opinion was expressed for the first time that vomiting conditions in infants are not isolated local conditions of the stomach or pylorus but pathologically conditioned corticovisceral reflexes. Habitual vomiting, pylorospasm and hypertrophic pyloric stenosis are varying degrees of the same disease. Hypertrophy of the musculature of the pylorus in hypertrophic pyloric stenosis is considered by the author to be the result of a prolonged disturbance of function and not the original cause of the disease. By giving a small amount of thickened food prior to each feed or nursing the peristaltic reflex of the stomach is established, the tendency to vomit is depressed, and a conditioned reflex in the Pavlovian sense is established which persists even after the thickened food is withdrawn. In this way vomiting ceases. This conception of vomiting in infancy makes it possible to prevent vomiting, particularly when a thorough attempt is made to eliminate external irritation.

The peristaltic function of the stomach is today generally accepted as an important factor in the pathogenesis of vomiting, and in the majority of pediatric textbooks the giving of a small amount of thickened food before feeding is recommended in the treatment. This confirms the correctness of the theoretical foundation and the significance of the reflex mechanism in the origin and treatment of vomiting conditions in infancy. FROM THE AUTHOR'S SUMMARY.

THE TREATMENT OF PERITONITIS. TOSOVSKY and L. HAVLUJOVA, Pediat. listy **7**:87, 1952.

A statistical analysis is made of 681 children treated for peritonitis during the years 1943 to 1949. The mortality was about 10% with the exception of the year 1945, when it attained 22.5%. It was decreased to 3.6% in the year 1949. The authors do not drain the peritoneal cavity and carry out primary suture. They place great stress on rehydration with plasma and blood and the full use of antibiotics, by which means they were able to decrease the mortality in 1949.

FROM THE AUTHORS' SUMMARY.

EXOMPHALOS. M. BRODSKY and E. FRYNTA, Pediat. listy **7**:91, 1952.

The origin and surgical treatment of exomphalos are described. A statistical analysis is given of 22 consecutive cases in which an operation was performed at the children's surgical ward in the course of the last ten years. Four cases are described in detail. A comparison is made of the results of the authors with the results reported in foreign literature, and in conclusion some suggestions are made with the aim of lowering the mortality among patients operated upon.

FROM THE AUTHORS' SUMMARY.

SUBCUTANEOUS AND CLOSED CONTUSIONS OF THE SMALL BOWEL IN CHILDREN. O. FRANK, Pediat. listy **7**:93, 1952.

Contusion of the small bowel arises as a result of a blow of considerable force to the abdominal wall. The only correct treatment is operative. Every person with injury to the abdomen must be admitted to hospital. The indications for operation usually arise later, since their cause is the slowly increasing contents of the bowels, which at first give rise to chemical irritation of the peritoneum and only later to infection. In doubtful cases operation is the lesser risk. Three cases are described in which operation was successful.

FROM THE AUTHOR'S SUMMARY.

Nervous Diseases

AN UNUSUAL CASE OF UNILATERAL EIGHTH NERVE TUMOR. V. H. MARK and W. H. SWEET, J. Neurosurg. **9**:395 (July) 1952.

The occurrence in the younger age group of bilateral acoustic tumor, or acoustic tumor associated with Recklinghausen's disease, or neurofibromatosis, is well known. Cushing stated that "a patient under 20 with a cerebellopontile-angle syndrome in all likelihood has a lesion other than an acoustic tumor."

The case of unilateral acoustic nerve tumor presented by the authors proves to be an exception to that rule, for the age of onset was 6 years and the neuroma was removed and the diagnosis verified histologically when the boy was 8½ years old. Furthermore, the patient showed none of the associated stigmas of Recklinghausen disease, as determined either by physical examination or from the family history. Other unusual features of this case include normal spinal fluid protein and massive destruction of the pyramid of the involved petrous bone.

ALPERS, Philadelphia. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CHRONIC NEUROLOGICAL DISEASE AS A POSSIBLE FORM OF LEAD POISONING. E. J. BUTLER, J. Neurol., Neurosurg. & Psychiat. **15**:119 (May) 1952.

It has long been known that the clinical manifestations of lesions in the nervous system produced by lead are diverse and may simulate the symptoms of various chronic neurological diseases. Early workers thought that lead might be an etiologic agent in such disease—for example, multiple sclerosis.

With improved analytical methods for the determination of lead, Butler studied four groups of patients: (1) 26 patients with multiple sclerosis and 5 patients probably affected with the disease; (2) 56 patients with other chronic neurological diseases, some of which, e. g., spastic paraplegia and peripheral neuritis, may be simulated by lead poisoning; (3) 7 patients with slight nonspecific symptoms, of whom 6 had experienced an occupational exposure to lead, and (4) 4 industrial workers with lead poisoning.

It was found that patients with multiple sclerosis showed no significant difference from those with other chronic neurological disease as regards their urinary excretion of lead and its concentration in the blood, cerebrospinal fluid, and tibial cortex, which in all patients was within the normal limits. For comparison, the patients with confirmed lead poisoning showed that an abnormally high urinary excretion of lead and coproporphyrin is maintained long after clinical remission and the disappearance of hematologic changes. The coproporphyrin excretion in the two groups of neurological patients was not significantly different, and with a few exceptions was within the normal range.

The administration of dimercaprol to neurological patients by injection consistently produced an increase in urinary lead excretion. This response in terms of increased lead excretion bore no apparent relation to the disease studied, nor did its magnitude indicate the presence of abnormal amounts of lead in the circulation and soft tissue. The lead content of necropsy samples of tissue, including the brain and spinal cord, obtained in cases in which the diagnosis of multiple sclerosis was confirmed histologically showed that lead was not responsible for the lesion in these cases and that there had been no mobilization of lead from the skeleton.

These studies do not support the view that lead plays a part in the etiology of multiple sclerosis and certain other chronic diseases of the nervous system.

ALPERS, Philadelphia. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

INSULIN, EPILEPSY, AND THE TEMPORAL LOBE. P. CASSA and P. MARTIN, Presse méd. **58**:1326 (Nov. 25) 1950.

In the treatment of schizophrenia with massive doses of insulin, seizures may be observed similar to epileptic attacks. Electroencephalographic studies which were carried on during a course of insulin treatment showed the presence of temporal lobe abnormalities typical of epilepsy. The authors warn against the use of insulin as a diagnostic agent in epilepsy, for fear of inducing epilepsy in apparently normal persons.

DAFFINEE, Melrose, Mass.

Psychology and Psychiatry

HELPING TEACHERS APPRECIATE EMOTIONAL PROBLEMS IN CHILDREN. HESS FARMER and WILLIAM B. ROSSMAN, Am. J. Psychiatry **108**:374 (Nov.) 1951.

Experiences in a mental hygiene workshop for teachers are described. The results indicate that the project is useful for teacher and pupil alike. It promotes an understanding in human relationships and better living in the classroom, and at the same time aids the teacher in a reorientation toward her own personal, social, and emotional problems.

JAHR, Omaha.

MENTAL CAPACITY OF THE CHILD. J. A. DE ARGUMOSA, Acta pediat. españ. **9**:694 (June) 1951.

In this work the author discusses the factors which influence the potential of mental development. The organic defects, either hereditary or acquired in early childhood, are first considered. Psychological influences include the emotional maturity and its development The culture or environment and family influences are the two remaining factors.

The author discusses the mechanism of many organic lesions and means of diagnosis. He mentions some of the work done in the biochemistry of the nervous system and the preliminary reports on glutamic acid. The revascularization operation of Beeck is described.

Dr. de Argumosa speaks of the need for changing the curriculum at schools and the proper use of psychological methods in dealing with children.

In the résumé he quotes from "The Intellectual Life," by P. Setillanges. "The teacher who burdens the memory is doing harm to the child's ability to think independently and to his attention span. The spirit is tired with the weight of such material and remains paralyzed. The dead weight oppresses that which wants to live. The excessive feeding intoxicates and we call these sufferers from such pretended erudition, however false and inert of spirit, 'living libraries' and 'walking dictionaries.'"

ALLEN, San Francisco.

Diseases of Genitourinary Tract

OSTEONEPHROPATHY IN CHILDREN. J. JAMES CANCELMO and RALPH S. BROMER, Am. J. Roentgenol. **65**:889 (June) 1951.

Osteonephropathy is a term used to designate certain closely related conditions in which there are bone changes associated with renal disease There are at least four distinct clinical syndromes characterized by alterations in the genitourinary, osseous, and endocrine systems. These are renal rickets, Fanconi's syndrome, nephrocalcinosis, and idiopathic hypercalciuria.

This paper presents a discussion of renal rickets and nephrocalcinosis with a report of eight cases of rickets and one case of nephrocalcinosis.

The majority of present-day investigators believe that renal rickets is primarily the result of renal insufficiency but that the parathyroid and the pituitary are secondarily involved. Kidney disease can be divided into three groups, (1) infection or inflammation, (2) congenital anomalies, and (3) obstructive uropathy.

The sequence of events in renal rickets is believed to be phosphorus retention due to renal damage, lowering of the serum calcium due to phosphorus retention, and subsequent parathyroid hyperplasia. Calcium is then removed from the bones in an effort to raise the serum calcium. Possible excretion of phosphorus in the intestines may interfere with calcium absorption. The pathologic changes in the bones include the bone lesions of osteitis fibrosa generalisata and the epiphyseal changes in children which roentgenologically closely resemble rickets.

Dwarfism is common. Failure to grow and gain weight with excessive thirst and polyuria may frequently be seen. These patients usually have moderate anemia, urine of low specific gravity, elevated nonprotein nitrogen and blood urea nitrogen, slightly depressed serum calcium and high serum phosphorus and alkaline phosphatase. The CO_2-combining power is usually low, indicating acidosis. The prognosis is not good.

Roentgenologically renal rickets manifests itself in the skeleton in several ways. There may be "rachitic changes" at the ends of the long bones which are indistinguishable from infantile rickets. The metaphyses may present a stippled, woolly, moth-eaten appearance. Subperiosteal

erosion of metaphyses is emphasized by the authors as a frequent finding in this disease. Retarded skeletal maturation is a common finding. Cyst formation in bone and metastatic calcification also occur.

"Nephrocalcinosis" is the term used to describe renal acidosis resulting from tubular insufficiency. The tubules lose the ability to make ammonia and excrete an acid urine. Because of this, fixed base in the form of calcium is excreted in the urine. Fall in the serum calcium produces parathyroid hyperplasia in an effort to raise the serum calcium. Raising the serum calcium permits phosphate diuresis, and hypophosphatemia results. Hypercalciuria is probably responsible for the nephrolithiasis which could produce glomerular damage and renal rickets. The distinguishing features of nephrocalcinosis are the low serum phosphorus, lack of evidence of glomerular damage, positive Sulkowitch test, and evidence of acidosis. X-rays demonstrate bone changes all the way from demineralization to marked rickets. Prognosis is good. Therapy is alkali replacement with sodium citrate and citric acid mixture plus calcium and vitamin D.

Renal rickets must be differentiated from rickets associated with celiac and biliary disease, vitamin-D-resistant rickets, and rickets found with other osteonephropathies. Cortical erosion or subperiosteal resorption of bone associated with hyperparathyroidism does not occur in nephrocalcinosis or in Fanconi syndrome. Primary hyperparathyroidism in persons under 14 years of age is extremely rare.

HODGSON, Rochester, Minn.

RENAL FUNCTION OF INFANTS DELIVERED OF TOXEMIC MOTHERS. D. C. A. BEVIS and S. F. SCHOFIELD, Arch. Dis. Childhood **26**:117 (April) 1951.

The renal function of infants delivered after maternal preeclampsia has been investigated and no change in the gross or microscopic anatomy of the kidney could be demonstrated. The urea clearances and the incidence of albuminuria are no different from those in normal babies, but the blood urea concentration is higher than normal. On the second day of life the toxemic babies are slightly hypertensive, but this difference has disappeared by the fourth day. An attempt is made to explain these findings by reference to Trueta's "shunt" theory of the renal circulation.

KELLY, Milwaukee.

CONGENITAL OBSTRUCTION OF THE POSTERIOR URETHRA. J. WAINWRIGHT, Arch. Dis. Childhood **26**:163 (April) 1951.

A case is reported of acute retention in a 2-month-old boy. This was due to a large cyst lying between the bladder and the rectum, believed to be derived from the prostatic utricle.

KELLY, Milwaukee.

CONSTITUTIONAL FACTORS IN THE NEPHROSIS SYNDROME. G. FANCONI, C. KOUSMINE, and W. FRISCHKNECHT, Helvet. paediat. acta **6**:199 (June) 1951.

The following observations suggest that constitutional factors play a role in the pathogenesis of the nephrotic syndrome.

1. It is a familial condition and may occur as a congenital abnormality. Until recently, only two families were known from the literature to substantiate this statement, but lately Prader has described occurrence of the nephrotic syndrome in uniovular twins, and three more families with concurrent nephrotic syndrome in siblings are reported in this communication.

Of six families investigated 13 children (12 boys and 1 girl) acquired the nephrotic syndrome at intervals of one to nine years. In families in which more than one child was affected the disease commenced each time at a characteristic age period (isochronism).

No explanation can be given for this familial occurrence of the disease. In the previous generations of the families investigated the nephrotic syndrome did not exist, and consanguinity could not be proved. The first-born always contracted the disease earlier and more severely than the later-born brothers or sisters.

2. The nephrosis syndrome is frequently coupled with an allergic diathesis. Of a total of 62 cases of nephrotic syndrome 27 (43.5%) showed signs of allergic diathesis. Two cases of nephrotic syndrome were associated with Feer's disease (acrodynia, pink disease), and in two other patients the syndrome developed after a mild-mercurous chloride treatment for worms;

two months after the initial treatment the clid fell ill with acrodynia. In Case 10 the treatment of myoclonus epilepsy with 0.3 gm. trimethadione three times daily for approximately eight months was followed by severe albuminuria. Three weeks later the nephrotic syndrome was fully developed. The child died 7 weeks afterward in spite of stopping use of the drug.

3. Of 62 patients with the nephrotic syndrome 82.25% contracted the disease under the age of 8, and 56.45% under the age of 4. Attention is drawn to the similarity in this respect to allergic reactions to mild mercurous chloride (Fanconi) and acrodynia (Feer's disease).

Age distribution is particularly striking when more than one child is affected in the same family, and it shows characteristic isochronism.

PROGNOSIS OF THE NEPHROSIS SYNDROME. G. FANCONI, C. KOUSMINE, and W. FRISCHKNECHT, Helvet. paediat. acta **6**:219 (June) 1951.

Sixty-two patients with the nephrotic syndrome were treated in the Children's Hospital, Zurich, beween 1913 and 1949.

The mortality was approximately 40% (24 patients). Eight of the deaths were due to pneumococcic infections of the serous cavities, a further eight succumbed to uremia, five died of cachexia and heart failure, and in three the cause of death could not be ascertained (patients died at home).

The nephrotic syndrome in children under the age of 4 is usually due to the pure form of lipid nephrosis; after that age, the nephrotic syndrome is often found combined with chronic glomerular nephritis.

The nephrotic syndrome may last two months or 18 years and the patient may make a complete recovery even after a period of illness lasting five years.

Seventeen patients in our series made a complete recovery (observation from 5 to 19 years), 12 were apparently healed (observation from 1 to 5 years), residual albuminuria was present in 6 cases, and 3 of the cases could not be traced in the follow-up.

GRULEE, Evanston, Ill.

NEPHROSIS SYNDROME IN CHRONIC INTRACAPILLARY GLOMERULONEPHRITIS. W. FRISCHKNECHT, C. WUNDERLY and G. FORSTER, Helvet. paediat. acta **6**:329 (Aug.) 1951.

A case of nephrotic syndrome with chronic intracapillary glomerulonephritis in a boy is described. The patient suffered 2½ years from generalized edema and ascites, severe proteinuria, cylindruria, lipiduria, extreme dysproteinemia, hypoelectrolytemia, slightly increased nonprotein nitrogen in serum and hypertension.

An angina [scarlet fever?] with repeated febrile attacks preceded this illness. The authors' treatment was unsuccessful. Death in uremia ensued after hospitalization for 14 months.

The pathogenesis of the edema and the enormous ascites (altogether 46.8 liters were removed by paracentesis), the proteinuria and the extreme dysproteinemia are discussed on the basis of a study of the membranes clinically from the formation of the transudates and the capillary resistance, and histologically by means of membrane staining of the glomerular capillaries; distribution of electrolytes between the serum and the ascitic fluid; electrophoresis of the serum before and after removal of lipids, as well as electrophoresis of the urinary proteins; specific absorption of the serum in the ultraviolet region; serologic typing of the serum proteins; extractability of the serum proteins in vitro, with reference to their disturbed function as a vehicle (e. g., for drugs), and an electrocardiogram during change of locations of the edema.

FROM THE AUTHORS' SUMMARY.

TRIDIMENSIONAL STRATIGRAPHIC STUDY OF THE BLADDER AFTER EXTRAPERITONEAL INSUFFLATION. G. SANSONE, N. MACARINI, and G. CORRADI, Minerva pediat. **3**:365 (June) 1951.

X-ray films are shown to illustrate the possibilities of transverse stratigraphy in a study of bladder pathology; the contrasting media of sodium bromide and insufflated oxygen combine to make the details very clear-cut.

HIGGINS, Boston.

PATHOGENESIS AND THERAPY OF ENURESIS NOCTURNA. W. LOHMÜLLER, Deutsche med. Wchnschr. **77**:622 (May 9) 1952.

The author thinks that, thanks to our knowledge of the vegetative nervous system, we are able to understand the functional events in cases of nocturnal enuresis. He proceeded to treat more than 200 patients with a preparation called "noxenur," which contains extract of Atropa belladonna and Ephedra vulgaris, vitamin B, and sodium glycerophosphate. One gram is equivalent to 1 mg. atropine salts. Excellent results were obtained in 90% of all cases.

AMBERG, Rochester, Minn.

PYURIA IN RELATION TO CONGENITAL MALFORMATIONS OF THE UROGENITAL TRACT. S. DREXLER and V. KAFKA, Pediat. listy **6**:96, 1951.

The authors stress the importance of early recognition of congenital malformations of the urinary system. Every child with pyuria (and hematuria) must be immediately hospitalized, and the complete urologic examination should follow.

Cases of acute exacerbations of chronic gastrointestinal affections should be suspected to be urological cases.

The authors have selected three interesting cases for publication, which should demonstrate the difficulties and possible mistakes in recognition and therapy of pyuria with congenital malformation of the urinary system.

To achieve satisfactory therapeutic effects early operative intervention is necessary; this at the same time reduces mortality and prevents the involvement of the renal parenchyma. The younger the patient is the better is the restitution of the organism, and therefore all operative interventions should be completed during the first years of life.

The authors call for conservative operative measures even in cases of unilateral affections, and nephrectomy should be performed only when it is unavoidable. The authors call for operative intervention in cases of bilateral affections as well.

In Case 1 a girl 3 months old had dystopic hydronephrosis, hydroureter and ureterocele with prolapse of ureter. Nephropexis was performed with good curative result.

In Case 2 a girl 6 months old had a double ureter on the right, hydroureter, and ureterocele on the right. After mobilization of the ureters and excision of the ureterocele nephropexis was performed with good result.

In Case 3 a boy 7 months old had stenosis ostiorum ureteralium, incipient ureterocele, hydronephrosis and hydroureter on both sides. Dilation of the ureteral opening on the right, nephropexis on the right, resection of the upper part of the right ureter, and pelvoureteral anastomosis were performed. The patient died three weeks after the last operation from sepsis.

FROM THE AUTHORS' SUMMARY.

Diseases of Ductless Glands; Endocrinology

PSEUDOHYPOPARATHYROIDISM AND HYPOPARATHYROID CRETINISM. H. ZELLWEGER and P. GIRARDET, Helvet. paediat. acta **6**:184 (June) 1951.

In 1940 Martin described a clinical syndrome for the first time which Allbright called pseudohypoparathyroidism. A further case is presented, of a girl who suffered from convulsions in infancy and in early childhood during the spring months. When she was 6 years old only a tetany with low serum calcium and high phosphorus was established. The calcium level improved transitorily with dihydrotachysterol, whereas parathyroid extract did not increase the urinary excretion of phosphorus. The lack of response to parathyroid was combined with the well-known symptoms of pseudohypoparathyroidism: short and thick-set body, round face, short neck, slight degree of oligophrenia, stammering, spikes and high 2 to 3 sec. waves in the electroencephalogram, and pachyderma.

A second case is presented with the same symptoms but without lack of response in the Ellsworth-Howard test. A similar case was presented earlier by Schupbach and Courvoisier, who call the above-described syndrome hypoparathyroid cretinism. Two forms of hypoparathyroid cretinism are to be distinguished, a form with negative Ellsworth-Howard test and a second with a clear response to parathyroid extract.

GRULEE, Evanston, Ill.

TREATMENT OF HYPERTHYROIDISM WITH CHOLINE HYDROCHLORIDE. A. DEGLI ESPOSTI, Clin. pediat. **33**:340 (June) 1951.

Twenty-three adults and one child with hyperthyroidism were given 1.0 or 1.5 gm. choline daily; 21 of the patients showed a gratifying relief of the symptoms and a lowered basal metabolism. When the medication had been discontinued for 15 to 20 days, the symptoms of hyperthyroidism returned. Resuming the medication led again to relief of symptoms. When 150,000 units of vitamin A were given daily to supplement the choline medication, the relief of the thyrotoxicosis was more prolonged.

Three groups of mice were studied. One group received thyroxin, the second thyroxin and choline, and the third choline. Histological examination of the thyroid glands of the first group revealed definite hypofunction, of the second group slight hypofunction, and of the third group hyperfunction.

The serum of patients who had received choline was found to protect tadpoles from the toxic effects of thyroxin.

The author concludes that choline acts mainly to neutralize the action of thyroxin, but also may inhibit the thyrotropic action of the pituitary gland.

HIGGINS, Boston.

EFFECTS OF GIVING THYMIC EXTRACT ON THE WEIGHT AND THE BLOOD PICTURE OF DYSTROPHIC INFANTS. E. GRASSO and G. BIZZI, Minerva pediat. **4**:72 (Feb. 15) 1952.

A deproteinized aqueous extract of thymus was given intramuscularly to 26 underweight children every two or three days; each child received between 4 and 21 injections. During the period of the injections, the weights of 17 of the children showed a marked increase, while the weights of the other 9 were essentially unchanged. In six of the children, there was a change in the blood picture toward a relative or absolute lymphocytosis. In eight of the children, there was an increase in the number of monocytes, a finding which suggests a stimulation of the reticuloendothelial system.

HIGGINS, Boston.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

CHRONIC POLYMYOSITIS. E. CHRISTENSEN and H. LEVISON, Acta psychiat. et neurol. **25**:137, 1950.

Christensen and Levison report on six patients with polymyositis without involvement of the skin. The patients included four women, of ages ranging from 16 to 38; a man aged 41, and a boy aged 9 years, probably stricken from birth. Three patients had a picture similar to that of progressive muscular dystrophy, with proximal atrophy and weakness of the limbs, and a typical waddling gait. Several patients had severe pains in the leg, thigh, or shoulder muscles. Generally the proximal muscle groups were affected. Muscle biopsy in all six cases showed inflammatory infiltration of the interstitial connective tissue with polymorphonuclear leukocytes, lymphocytes, plasma cells, and a few eosinophiles. In four cases the round cell infiltration was chiefly perivascular, and in two cases it was very diffuse. The muscle fibrils in the individual bundles showed irregular atrophy. Electromyography in five cases indicated some type of myogenic disorder. The creatinine output was increased in four patients and normal in one. Treatment consisted of administration of large amounts of penicillin or streptomycin. In a patient treated with penicillin there was an exacerbation, with death following acute myocarditis. In three patients treated with streptomycin there seemed to be some effect on pain, atrophy and paresis.

PISETSKY, New York [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Cutaneous Diseases; Allergy

THE ALIMENTARY LESION IN ANAPHYLACTOID PURPURA. C. L. BALF, Arch. Dis. Childhood **26**:20 (Feb.) 1951.

The alimentary lesion in anaphylactoid purpura is described, and five illustrative cases are reported in detail. It is suggested that in anaphylactoid purpura local vasospasm is responsible for the segmented lesions in the bowel, such vasospasm being secondary to damage of the arterioles.

KELLY, Milwaukee.

UNCOMMON DRUG RASHES. G. A. GRANT PETERKIN, Edinburgh M. J. **58**:42 (Feb.) 1951.

Considering the vast quantities of medicines consumed by the patient on his own initiative or on the advice of physicians, it is surprising that drug rashes are uncommon; about 1 in every 2,000 hospitalized patients. Some drug eruptions are due to skin sensitization, but many are not allergic in origin; they may be caused by toxins liberated from a septic focus—e. g., erythema nodosum or erythema multiforme after treatment of streptococcic sore thoat with sulfonamides—and they may be due, in part at least, to hypovitaminosis—e. g., lichenoid dermatitis due to quinacrine and sulfonamide light dermatitis.

The dermatoses caused by drugs may take many forms and can mimic almost every kind of skin disease. Lesions closely resembling such diverse conditions as lupus erythematosus, acne vulgaris, and malignant tumors can be due solely to drugs. One of the most curious forms of dermatitis medicamentosa is the fixed drug eruption, which may be caused by many drugs. In this eruption oval edematous plaques of different sizes recur on various parts of the body. They may itch and burn. These patches, dusky red at onset and with definite borders, sometimes progress to form bullae. Desquamation appears as the eruption fades, leaving pigmentation of variable shades and duration. There is a tendency for the eruption to relapse in situ.

Peterkin has selected several drugs for illustration. They are outlined below with the characteristic eruptions listed first, followed by less common types of eruption that may be associated with the individual drug.

I. Phenolphthalein
- (*a*) Fixed drug eruption
- (*b*) Localized pruritus
- (*c*) Erythema multiforme
- (*d*) Pseudoepitheliomatous hyperplasia

II. Barbiturates
- (*a*) Morbilliform eruptions
- (*b*) Scarlatiniform eruptions
- (*c*) Purpuric eruptions
- (*d*) Erythema multiforme
- (*e*) Fixed drug eruption
- (*f*) Generalized pruritus
- (*g*) Stevens-Johnson disease
- (*h*) Rashes resembling lupus erythematosus and tinea corporis

III. Quinine
- (*a*) Scarlatiniform eruption
- (*b*) Eczema
- (*c*) Melanoderma

IV. Quinacrine
- (*a*) Morbilliform eruption
- (*b*) A rash that begins as eczema, and then develops vesicles or bullae; in some instances this eruption acquires the appearance of lichen planus

V. Heavy Metals, E. G., Gold, Arsenic, Bismuth, and Mercury
- (*a*) Fowler's solution by mouth can produce edema of the face and, after prolonged administration, dappled pigmentation, as well as keratoses that may progress to carcinoma
- (*b*) Given by injection, these metals may simulate any skin disease, e. g., eczema, scarlatina, purpura
- (*c*) Acrocyanosis with erythema and swelling of palms and soles; may be caused by arsenic, gold, or mercury

VI. Sulfonamides
- (*a*) Seborrhea with photosensitivity
- (*b*) Lupus erythematosus
- (*c*) Erythema multiforme
- (*d*) Erythema nodosum
- (*e*) Pemphigus
- (*f*) Morbilliform, scarlatiniform, acneform, and purpuric rashes

VII. Paraaminosalicylic acid
- (*a*) Scarlatiniform rashes
- (*b*) Fixed drug eruption
- (*c*) An eruption resembling sulfonamide light dermatitis

VIII. Antibiotics

A. Penicillin
- (*a*) Urticaria
- (*b*) Eczema
- (*c*) Erythematopapular and vesicular eruptions
- (*d*) Erythema nodosum
- (*e*) An eruption similar to sulfonamide light dermatitis
- (*f*) Reactivation of dormant fungous infection

B. Streptomycin
- (*a*) Roseolar eruption
- (*b*) Maculopapular eruption
- (*c*) Morbilliform or scarlatiniform eruptions
- (*d*) Urticaria
- (*e*) Follicular dermatitis
- (*f*) Erythema multiforme

C. Aureomycin
- (*a*) Urticaria
- (*b*) Eczema
- (*c*) Generalized desquamation
- (*d*) Erythema nodosum

IX. Antihistamines
- (*a*) May cause reactions similar to those of sulfonamides

MACDONALD, Pittsburgh.

HYPERPROTEINEMIA AND THE SYNDROME OF KWASHIORKOR. DUIS TORRES MARTY, Acta pediat. españ. **9**:703 (July) 1951.

The author presents some cases previously studied. Kwashiorkor syndrome is characterized by alteration of hair, which is fine, long, but rather scarce; there are edema, especially in the lower extremities, enlarged abdomen, diarrhea, and, in most cases, pigmentary changes in the skin. There are definite hypoproteinemia and an inversion of the serum-globulin ratio.

The differential diagnosis is made between this condition and acrodynia, pellagra, and riboflavin deficiency. The author feels there may be some relation as yet undiscovered between this syndrome and celiac disease and cystic fibrosis of the pancreas.

He also toys with the idea that it may have some connection with erythroblastosis fetalis in infants.

The clinical history reveals poor nutrition and health habits and a poor family constitution.

Treatment is effective if it includes transfusion, plasma therapy, rational dietary control, and administration of liver extract.

ALLEN, San Francisco.

ACRODYNIA, MERCURY, AND DIMERCAPROL. P. DENYS, Acta pædiat. belg. **4**:16, 1950.

Recent publications have indicated that mercury may be the causative agent in acrodynia. The author takes issue with this assumption by critically analyzing the literature and presents six cases of Feer's disease. In this group only two had previous treatment with mercury. Abnormal quantities of mercury in the urine were found in four of the six patients. Three patients treated with dimercaprol showed no benefit. The author feels that, although mercury may play a role in some cases of acrodynia, it has not been established that mercury is the direct cause of the disease.

GLASER, Jerusalem.

REPORT OF A CASE OF STEVENS-JOHNSON SYNDROME. SCHELLINCK and WASTELAIN, Acta pædiat. belg. **4**:256, 1950.

A 6-year-old boy was treated with sulfonamides for otitis media. Nine days after the fever had subsided, a new attack of fever occurred, this time with morbilliform eruption of the skin, stomatitis, and inflammation of conjunctiva and nasal mucosa. During the next few days, the skin eruption showed vesiculation and desquamation of large areas. The authors point out that this condition affects infants and young children, predominantly boys. Etiologically they consider either bacterial or viral infection or allergy. Sensitization to sulfonamides in the presented case could have been produced during the treatment of the otitis preceding the appearance of the Stevens-Johnson syndrome. It is remarkable that the child's father had desquamative erythroderma following a gold treatment some 15 years previously.

GLASER, Jerusalem.

MALHERB'S EPITHELIOMA. J. SVEJDA, Pediat. listy **7**:106, 1952.

Three cases of Malherb's epithelioma in children are described and the question of their origin briefly discussed. The epithelioma is a hamartoma, either congenital or acquired, arising from the transition of a benign nevus to an epitheliomatous and basalomatous nevus. The tumor is benign but has a certain slight malignant potential in that it may rarely be subject to malignant degeneration.

FROM THE AUTHOR'S SUMMARY.

Teeth and Dentistry

DENTAL CARIES IN THE COTTON RAT: XIII. THE EFFECT OF WHOLE GRAIN AND PROCESSED CEREALS ON DENTAL CARIES PRODUCTION. MARGUERITE A. CONSTANT, PAUL H. PHILLIPS and C. A. ELVEHJEM, J. Nutrition **46**:271 (March 10) 1952.

When fed under similar conditions, the whole grain cereals, corn, wheat, and oats, were found to be less cariogenic in each case than their processed products, corn flakes, wheat flakes, and oatmeal, respectively. Natural diets which contained processed cereals and only 30% sugar were found to be more cariogenic than a synthetic diet containing 67% sucrose. A significant difference was not found between the cariogenicity of alkaline-ash and that of acid-ash foods under the experimental conditions used.

FREDEEN, Kansas City, Mo.

Surgery and Orthopedics

ACTH (CORTICOTROPIN) IN BURNS. I. VAN DER HAL and J. W. R. EVERSE, Maandschr. Kindergeneesk. **19**:157 (July) 1951.

In severe burns the adrenal gland plays an important part in the reactions of the body, according to Selye's views. From indications in the literature it can be presumed that either an exogenic supply of 11-hydroxysteroids of the cortisone type or administration of corticotropin so as to stimulate continuously the patient's own adrenal cortex may have a favorable influence.

The favorable experiences in the treatment with corticotropin (ACTH) of a 4-year-old child who had sustained severe burns and was in a state of acute shock were in agreement with this view.

During administration of corticotropin a decreased resistance to infections is likely to exist. The child treated by the authors contracted bronchopneumonia during corticotropin administration. Probably the use of corticotropin in burns must be considered only if the prognosis is very unfavorable without it. Simultaneous administration of antibiotics seems necessary.

As appears from American reports, corticotropin may also be used in the later stages of the healing process, as it inhibits granulation and thus counteracts scar formation.

FROM THE AUTHORS' SUMMARY.

Miscellaneous

FERROUS SULFATE POISONING. THOMAS L. DUFFY and ANTONI M. DIEHL, J. Pediat. **40**:1 (Jan.) 1952.

Ferrous sulfate poisoning starts with vomiting and retching and clear watery stools that later become tarry. The picture is one of profound shock and collapse with rapid weak or imperceptible pulse, low blood pressure, hypotonia, and hyporeflexia, dilated pupils, and stupor or coma. Immediate treatment with plasma and/or whole blood is imperative. One of the three patients reported here died.

MACDONALD, Pittsburgh.

FERROUS SULFATE POISONING. SHERROD C. SWIFT, VICTOR CEFALU, and EARL B. RUBELL, J. Pediat. **40**:6 (Jan.) 1952.

High concentrations of ferrous sulfate in the small intestine necrotize the mucosa, the normal barrier to iron. Then, essentially unaltered iron salts enter veins and lymphatics, producing thrombosis and gangrene. The resultant toxemia may produce extensive liver damage and visceral hemorrhage. Methemoglobinemia, previously reported, was absent here. This patient had an initial period of shock, intermediate period of relative recovery, and then sudden death.

MACDONALD, Pittsburgh.

DIAGNOSIS AND TREATMENT OF UNUSUAL CONDITIONS IN INFANTS AND CHILDREN. JOHN L. REICHERT, Illinois M. J. **99**:197-203 (April) 1951.

Dr. Reichert reports and discusses five unusual conditions culled from the records of the Children's Memorial Hospital of the past five years.

1. A case of congenital functional intestinal obstruction simulated a clinical picture of obstructive ileus. No anatomic obstruction was found at operation. Instead there was a narrowing of the affected segment which contained fecal impaction and showed no peristaltic motility. There was dilatation and hypertrophy of the colon proximal to this area. Barium should not be given by mouth in preoperative studies of these cases because of the fecal impaction which occurs.

2. A case of hypertensive encephalopathy was presented not so much because of its rarity, but because of the difficulty in distinguishing this complication of childhood nephritis from two other complications, cardiac failure and renal failure. The confusion lies in the initial emergency procedures, which often require the most careful judgement.

3. Spontaneous subluxation of the cervical spine consists of a fusion (apparently congenital) of the atlas and the axis. Reichert believes that it would seem advisable to apply traction in any case of sudden, spontaneous torticollis associated with an upper respiratory infection, with severe pain, tenderness, and muscle spasm of the upper posterior area of the neck, which does not respond to heat and antibodies in a few days. This procedure might make the difference between recovery and permanent deformity or death.

4. In congenital esophageal atresia with tracheoesophageal fistula the clinical picture is distinctive and uniform. The author urges early recognition of this condition, the use of iodized poppyseed oil (not barium) in the esophagus, proper preoperative care and preparation, and surgery as soon as possible.

5. A case of lung abscess illustrates three things: 1. Infants with infections often do not have the usual signs of infection as seen in older children, such as fever, abnormal white cell count, and loss of weight. 2. The antibiotics can mask a disease without curing it. 3. While

the contemplation of unusual conditions in medicine is an interesting pursuit, we must give due prominence in our considerations to the common diseases if we wish to maintain a high percentage of correct diagnoses.

BARBOUR, Peoria, Ill.

ABSORPTION OF ALPHA-TOCOPHEROL AND TOCOPHERYL ESTERS BY PREMATURE AND FULL-TERM INFANTS AND CHILDREN IN HEALTH AND DISEASE. LLOYD J. FILER JR., STANLEY W. WRIGHT, MARY PARKE MANNING, and KARL E. MASON, Pediatrics **8**:328 (Sept.) 1951.

The ability of premature and full-term infants in health and disease to absorb vitamin E (tocopherol) was determined using the technique of multiple withdrawals of small samples of capillary blood at three-hour intervals following an oral dose of α-tocopherol or α-tocopheryl esters.

Premature infants were found to absorb vitamin E as well as full-term infants, when compared on the basis of the area under the curve for a 12-hour period following an oral dose of tocopherols at 20 mg. per kilogram of body weight. This is in marked contrast to the diminished ability of the premature infant to utilize vitamin A and fats.

In a series of 29 infants, those disease states diagnosed as fibrocystic disease of the pancreas, diarrhea, and cirrhosis were characterized by a poor response to the test; i. e., the tolerance curve was low. Others, infants with a variety of disorders not associated with intolerance of fat or fat-soluble vitamins, had characteristic absorption curves with a maximum nine hours after receiving tocopherol orally.

In a series of 14 children and 1 adult, patients with sprue, celiac syndrome, and lupus erythematosus absorbed tocopherols poorly. Metabolic disorders with associated hypercholesterolemia were observed to give abnormally high values for the area under the curve.

A comparison of vitamin-A absorption with vitamin-E or tocopherol absorption in a series of 10 observations indicated that patients responding poorly to one test did poorly in both.

No difference in response was noted when various esterified forms of tocopherol were administered in place of α-tocopherol. This is contrary to the reported increase in biologic potency (rat assay) of the esterified forms of tocopherol.

An index calculated from the fasting and nine-hour levels of serum tocopherol which was corrected for the tocopherol equivalents supplied by the ester forms compared favorably with the area measurements and failed to demonstrate any difference in absorption of the free versus the ester tocopherol.

FROM THE AUTHORS' SUMMARY.

"GROWING PAINS": A CLINICAL STUDY OF NON-ARTHRITIC LIMB PAINS IN CHILDREN. JOHN M. NAISH and JOHN APLEY, Arch. Dis. Childhood **26**:140 (April) 1951.

By sampling, the incidence of persistent nonarthritic limb pains in the Bristol school population was found to be 4.2%. It was approximately equal in boys and girls, and the maximum incidence lay between 8 and 12 years of age.

By comparison with controls, a family history of rheumatic disorders was found to be significantly commoner in children with such pains. Minor emotional disturbances also appeared to be common, especially in certain groups.

The majority of children with limb pains fell into one of two groups. "Diurnal fatigue pains" occurred in children in association with exertion, fatigue, and postural defects. In this group emotional disturbances were very common, and there was a strong family history of rheumatic disorders. "Paroxysmal nocturnal pains" occurred in children who were more stable emotionally but who came from families in whom similar pains were common. A small group of children had pains apparently of psychological origin without other association.

KELLY, Milwaukee.

FEBRILE REACTIONS TO PARAAMINOSALICYLIC ACID. B. KREIS, A. LIBERT, F. PAQUELIN, and J. ABRIC, Presse méd. **58**:1285 (Nov. 18) 1950.

The authors describe a number of febrile responses to the use of paraaminosalicylic acid in the treatment of tuberculosis. In some of the patients, the development of the fever was slow and progressively severer, while in others the fever appeared as acute episodes suggesting exacerbations of the tuberculous process.

DAFFINEE, Melrose, Mass.

MATERNAL AND CHILDREN'S HOSPITALS IN SPAIN. JUAN BOSCH MARIN, Acta pediat. espan. **9**:415 (April) 1951.

Dr. Marin gives the report of a survey of facilities for caring for mothers and babies in all of Spain. The report is made to the maternal and infant-care section of a public health meeting in April, 1951.

Since the organization of this group, mortality rate of infants under 1 year has fallen from 103 per 1,000 live births to 62.72 per 1,000 live births, in other words, from one of the worst to one of the best in Europe despite revolution, war, and the after-effects of war.

The author gives credit to certain privately organized groups for their educational work and to national and provincial organizations on the professional level. The deaths from infectious diseases other than enteritis, however, account for most of the falling mortality rate. The deaths from enteritis, dysentery, and prematurity are still too high.

The maternal death rate also has not fallen as it should, and only in the larger cities are there adequate facilities for maternal care during pregnancy and at delivery.

There should be better coordination, also, between the various types of hospitals and better techniques and equipment in some of the older institutions.

Tables on distribution of beds for obstetrics and pediatrics are given with the following classifications: (1) name of province; (2) population, 1950; (3) number of births; (4) number of hospital deliveries; (5) number of abnormal cases (medically); (6) number of abnormal cases laid to social and economic reasons, and (6) total beds.

In the pediatric survey, the following classifications are noted: (1) province; (2) population from birth to 14 years; (3) beds for acute cases; (4) beds for tuberculosis cases, and (5) charity beds and total beds.

Maps of each province showing location of hospitals and difficulties of transportation to a medical center are also included.

To summarize, the population of 29,000,000 Spaniards have available only 6,190 beds for maternity cases. There were 32,130 cases involving some medical abnormality and 128,387 which for economic or social reasons presented some difficulty at the time of delivery in the hospital which prenatal care might have prevented.

There are 4,015 beds for acutely ill children, 4,015 for chronic children's diseases located in provincial capitals only, and 1,975 beds for convalescent and crippled children, but also only in capitals. The total number of pediatric beds for a child population of 6,992,468 is 10,005.

The maps show the locations of all of these facilities. ALLEN, San Francisco.

POLYAGGLUTINABILITY OF ERYTHROCYTES IN A CASE OF PNEUMOCOCCIC MENINGITIS. L. HOLLÄNDER, Helvet. paediat. acta **6**:149 (April) 1951.

A baby of 11 months suffering from pneumococcic meningitis showed polyagglutinability of the red blood cells. The phenomenon leads to a wrong blood-group determination; this is followed by a transfusion reaction after repeated transfusions. Ninety-five per cent of all samples of serum were found to agglutinate the baby's red blood cells; the only serums that did not agglutinate were those derived from babies and infants whose blood does not possess any anti-T agglutinins. The presence of anti-T agglutinins can be demonstrated by elution technic in saline solution. The relationship of polyagglutinability to the Hübener-Thompsen-Friedenreich phenomenon and the theory of a receptor-destroying enzyme (Burnet) are taken into consideration.

FROM THE AUTHOR'S SUMMARY.

NEW BIOLOGICAL METHOD FOR DOSAGE OF VIOMYCIN. ALVARO MASI and PIERO MOGGI, Rev. clin. pediat. **49**:585 (Aug.) 1951.

A biological method for the dosage of viomycin, employing Pergola's dishes with medium inoculated on the surface with Corynebacterium diphtheriae, is described. This method, founded on the measurement of the inhibition haloes, is easily accomplished and adequately sensitive.

FROM THE AUTHORS' SUMMARY.

SOME IDEAS ABOUT THE USE OF GLUCOSE ORALLY. G. VIDAL JORDANA, Acta pediat. españ. **99**:253-264 (March) 1951.

Dr. Jordana reviews the functions of glucose in the body's economy; since glucose is more readily absorbed in the infant by mouth than by subcutaneous injection, it should be used more widely in this manner in acutely ill babies. It has the advantage also of being less likely to cause fermentation than are the more complex carbohydrates. He feels that many clinicians fearing the fermentation of carbohydrate diet in diarrheas, for example, have been too timid in the use of glucose by mouth.

He gives four case histories with vomiting due to pylorospasm, malnutrition, dehydration, and acidosis in which no gain in weight or appreciable improvement occurred until a 10% glucose solution with amino acids was given by mouth. Heroic measures, including blood transfusions, had kept the child alive. The addition of the glucose and amino acids by mouth gave a sense of well-being, and the weight increased steadily. In all these cases the feeling had been artificial and the vomiting of a serious nature, and yet glucose was retained. All patients were under 1 year.

Acute hepatitis, which is common in children, responds well to this type of feeding, and in most diseases of the liver in which the glycogen has become depleted, 10% glucose solution by mouth helps restoration of the glycogenic function. Even in glycogenosis hepatica, or Gierke's disease, in which the liver is overloaded with glycogen, the glycogen is not easily mobilized and hypoglycemia is also present. These patients may require adrenal extract, 50 to 100 gm. of glucose by mouth or, in serious cases, dextrose intravenously.

ALLEN, San Francisco.

News and Comment

GENERAL NEWS

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., after examinations held in Baltimore on Feb. 20, 21, and 22, 1953:

Abelman, Lester M., Belmont, Mass.
Apt, Leonard, Boston.
Arnold, Gayle Gardner, Richmond, Va.
Ashbey, Dwight Ransford, Jr., Lancaster, Pa.
Balakrishnan, Subrahmanya, Toronto, Canada.
Bass, Lee Weil, Pittsburgh.
Bauman, William Allen, New Rochelle, N. Y.
Benbow, Edward P., Jr., Greensboro, N. C.
Blatt, Norman H., Chicago.
Bookhalter, Ethel Mina, New York.
Brown, Geo. W., Tyler, Texas.
Burke, Robert John, St. Louis.
Capute, Arnold John, Brooklyn.
Cardullo, Hugo, M., Brooklyn.
Casden, Daniel D., Valley Stream, N. Y.
Cassidy, John Edward, Bethesda, Md.
Cherwitz, Gordon, Providence, R. I.
Connor, Hilary H., Providence, R. I.
Crawford, Robert P., Camp Kilmer, N. J.
Day, Lewis Robbins, Denver.
Diehl, Antoni Mills, Great Lakes, Ill.
Duggan, John A., Cambridge, Mass.
Eney, R. Donald, Baltimore.
Faber, Kalman, Philadelphia.
Firpi, Miguel A., Santurce, Puerto Rico.
Folston, Mortimer James, Washington, D. C.
Forney, Willard E., San Pedro, Calif.
Freda, Franklin D., Newark, N. J.
Fryer, Harry J., Charlestown, Md.
Gedarovich, Albin, St. Albans, L. I., N. Y.
Glick, Herbert D., Silver Spring, Md.
Green, Marvin, Bayside, N. Y.
Gribetz, Donald, Boston.
Haggard, Carl Newton, Houston, Texas.
Harrington, Francis J., Milton, Mass.
Hazen, Lloyd Norman, Weymouth, Mass.
Hessel, Marianne, Redondo Beach, Calif.
Horton, Frank Hamilton, Great Lakes, Ill.
Husson, Patricia H., Baltimore.
Irvin, Robert A., Painseville, Ohio.
Jaslow, Robert I., Chambersburg, Pa.
Jenkins, Joseph Clay, Euclid, Ohio.
Johnston, Ian Bruce, Lafayette, Calif.
Kaplan, Solomon, A., Cincinnati.
Kershner, Richard Dudley, Camp Lejeune, N. C.
King, Harry, New York.
Knaus, William E., East St. Louis, Ill.
Kresock, Joseph W., Springfield, Mass.
Lesser, Leonard I., Tuscaloosa, Ala.
Levbarg, Morrison S., New York.
McCarthy, Frank W., Jr., Hartford, Conn.
McNamara, Dan Goodrich, Baltimore.
Mendez, Dolores I., Santurce, Puerto Rico.
Mervis, Jacob, Steubenville, Ohio.
Michaud, J. Ellery, Fall River, Mass.
Miller, Robert Treadwell, Arlington, Va.
Murphy, James William, Langley Air Force Base, Va.
Murphy, William Francis, Jr., Norfolk, Va.
Nash, Helen Elizabeth, St. Louis.
Newton, Robert F., San Antonio, Texas.
Nottingham, Robert J., Morgantown, W. Va.
O'Connor, Walter Joseph, Brooklyn.
Orme, Robert J., Norwood, Mass.
Oshman, Joseph, Corpus Christi, Texas.
Paine, Richmond Shepard, Boston.
Paradise, Jack Leon, Bellaire, Ohio.
Pasquariello, Peter J., N. J.
Pearson, Paul Hammond, Baltimore.
Pomeroy, Stuart A., Syracuse, N. Y.
Potter, Howard John, Lexington, Mass.
Richards, Mary Robinson, Teaneck, N. J.
Rosenzweig, Leonard F., Freeport, N. Y.
Rutzky, Julius, Detroit.
Schaefer, Franklin H., Gallipolis, Ohio.
Schreiner, Gilbert C., Bryan, Texas.
Siddoway, John Lewis, Jr., Salt Lake City, Utah.
Snyder, Maurice Elwyn, Ayer, Mass.
Stewart, Lula Belle Therese, Jackson, Miss.
Sweeney, Michael James, Snyder, N. Y.
Tanner, Megan, Danville, Ill.
Twible, Ellsworth Arnold, N. Weymouth, Mass.
Waldron, Robert John, Norfolk, Va.
Walker, Maggie Laura, Chicago.
Walker, Stuart H., Fort Meade, Md.
White, Forrest, P., Norfolk, Va.
Whittemore, Ruth, New Haven, Conn.
Woodard, William Kay, Lualualei, Oahu, T.H.
Wooding, Clinton Hannix, Jr., Norfolk, Va.
Zweifler, Ben M., Brooklyn.

Pediatricians Certified in Pediatric Allergy by the American Board of Pediatrics, Inc.—The following pediatricians were certified in the subspecialty of pediatric allergy at the examination held in Boston on Feb. 25, 1953:

Walter Richard Kessler, New York.
Abe Matheson, Chicago.
Roland Boyd Scott, Washington, D. C.
Sheldon C. Siegel, St. Paul.
Samuel Untracht, New York.
Ross R. Weller, Milwaukee.

ANNUAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION

New York, June 1-5, 1953

The following portion of the program of the American Medical Association Scientific Session relating to pediatrics will be of interest to readers of this Journal.

SECTION ON PEDATRICS

GRAND BALLROOM, COMMODORE HOTEL

Tuesday, June 2—2 p. m.

JOINT MEETING WITH SECTION ON RADIOLOGY

Emergencies in the Newborn
GEORGE COOPER JR., MCLEMORE BIRDSONG, and RANDOLPH BRADSHAW, Charlottesville, Va.
Discussion to be opened by FRED H. WILKE, New York

Physiological Bowing of the Legs in Young Children
JOHN F. HOLT and HOWARD B. LATOURETTE, Ann Arbor, Mich.
Discussion to be opened by KENNETH D. A. ALLEN, Denver

Specificity of Roentgen Findings in Suppurative Pneumonia of Infants and Children
J. A. CAMPBELL and DAVID C. GASTINEAU, Indianapolis
Discussion to be opened by FRED JENNER HODGES, Ann Arbor, Mich.

Hirschsprung's Disease: The Roentgen Diagnosis in Infants and Young Children
RAYMOND G. MCDONALD and WILLIAM E. EVANS, Detroit
Discussion to be opened by GEORGE P. KEEFER, Philadelphia

Cholecystography During the First Months of Life
JOHN CAFFEY and RUTH HARRIS, New York
Discussion to be opened by FREDERICK N. SILVERMAN, Cincinnati

Lesions of the Esophagus in Infancy EDWARD B. D. NEUHAUSER, Boston
Discussion to be opened by WILLIAM H. SHEHADI, New York

Wednesday, June 3—2 p. m.

BUSINESS MEETING
ELECTION OF OFFICERS

Chairman's Address EUGENE T. MCENERY, Chicago

Symposium on Prevention of Needless Neonatal Deaths

From the Viewpoint of the Public Health Officer HERMAN N. BUNDESEN, Chicago
Discussion to be opened by JOSEPH G. MOLNER, Detroit, and SAMUEL M. WISHIK, Pittsburgh

From the Viewpoint of the Hospital Administrator CHARLES U. LETOURNEAU, Chicago
Discussion to be opened by ANTHONY J. J. ROURKE, New York

From the Viewpoint of the Pediatrician STEWART H. CLIFFORD, Brookline, Mass.
Discussion to be opened by SAMUEL Z. LEVINE and LEONA BAUMGARTNER, New York

From the Viewpoint of the Obstetrician CARL F. HUBER, Indianapolis

Discussion to be opened by CARL GOLDMARK JR., New York, and NICHOLSON J. EASTMAN, Baltimore

Thursday, June 4—2 p. m.

JOINT MEETING WITH SECTION ON PHYSICAL MEDICINE AND REHABILITATION AND SECTION ON PREVENTIVE AND INDUSTRIAL MEDICINE AND PUBLIC HEALTH

RUTHERFORD T. JOHNSTONE, Los Angeles, Presiding

Address of Chairman of Section on Preventive and Industrial Medicine and Public Health VLADO A. GETTING, Boston

Epidemiologic Aspects of the Uses of Gamma Globulin in Poliomyelitis JOSEPH A. BELL, Bethesda, Md.

National Policies Relative to the Distribution of Gamma Globulin W. H. AUFRANC, Washington, D. C.

Present Status and Future Possibilities of Vaccine for the Control of Poliomyelitis ALBERT B. SABIN, Cincinnati

Differential Diagnosis of Poliomyelitis CLIFFORD G. GRULEE JR., New Orleans

Treatment of Acute Phase of Poliomyelitis ALEX J. STEIGMAN, Louisville, Ky.

The Early Treatment of Poliomyelitis JESSIE WRIGHT, Pittsburgh

Discussion to be opened by DUANE A. SCHRAM, Gonzales, Texas

Rehabilitation in Poliomyelitis ROBERT L. BENNETT, Warm Springs, Ga.

Discussion to be opened by MORTON HOBERMAN, New York

ANNOUNCEMENTS

Coming Examinations to Be Held by the American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc., will hold oral examinations on May 1, 2, and 3, 1953, in Philadelphia.

Nassau Pediatric Society.—The next scientific meeting of the Nassau Pediatric Society will be held at the Garden City Hotel on April 13, 1953, at 9 p. m. Dr. Maclyn McCarty, from the Rockefeller Institute for Medical Research, will be the guest speaker. His topic for the evening will be "The Diagnosis of Rheumatic Fever and Evaluation of Activity of the Disease."

The June meeting will be held on the evening of June 15th, instead of June 8th as originally scheduled.

New Children's Hospital.—The trustees of the Robert Driscoll, Julia Driscoll, and Robert Driscoll Jr. Foundation of Corpus Christi, Texas, announce the formal opening of the Driscoll Foundation Children's Hospital on Feb. 22, 1953. This 110-bed hospital is the nucleus of the foundation's efforts to establish the highest quality of medical and surgical service without cost for needy children in southwestern Texas.

Participating in the dedication ceremony were Dr. Arild Hansen of Galveston, Texas, and Dr. Fred H. Howard, medical Director of the new hospital.

Refresher Course in Pediatrics.—A refresher course in pediatrics will be conducted at St. Christopher's Hospital for Children, Philadelphia, by the Department of Pediatrics of Temple University School of Medicine on June 10 to 13, 1953. Each half-day session will be devoted to a single phase of pediatric medicine. For information regarding enrollment, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia 33.

International Catholic Child Bureau.—Carrying on its series of international congresses on the main topics of childhood, the International Catholic Child Bureau will hold its fourth congress at Constance, Germany, from May 4 to 9, 1953.

University of California Medical Department, Los Angeles, Assumes Control of Marion Davies Children's Clinic.—The Department of Pediatrics of the University of California Medical Department at Los Angeles recently assumed control and operation of the Marion Davies Children's Clinic, Los Angeles. This clinic is a general pediatric clinic with appropriate subdivisions devoted to the care of sick infants and children in southwestern United States. Until the University Hospital of the new University of California Medical Department is completed in 1954, pediatrics will be taught to the medical students at this clinic. Applications for pediatric internship and residency are now being accepted.

Directory of Pediatric Societies *

INTERNATIONAL

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 16, rue du Mont-Blanc, Geneva, Switzerland.
Place: Bombay, India. Time: Dec. 5-12, 1952.

IV° Congreso Pan-Americano de Pediatria

President: Dr. Leonel Gonzaga.
General Secretary: Dr. Adamastor Barbosa.
Secretariat: Rua Dias da Rocha 25, ap. 602, Copacabana, Rio de Janeiro.
Place. Rio de Janeiro. Time: 1954.

IV° Congreso Sudamericano de Pediatria, Confederacion Sudamericano de Sociedades de Pediatria

President: Prof. Carlos Prado.
Vice President: Dr. Marcelo Garcia.
General Secretary: Dr. Alvaro Aguiar.
Place: Avenida Mem de Sá 197, Rio de Janeiro. Time: 1954.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. Bernard Laski, Toronto.
Secretary: Dr. Crawford Anglin, Toronto.
Place: Academy of Medicine.

Australian Paediatric Association

President: Dr. Robert Southby.
Secretary: Dr. J. Colebatch, 12 Collins St., Melbourne.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Prof. J. Smellie.
Secretary: Prof. Alan Moncrieff, Institute of Child Health, The Hospital for Sick Children, Great Ormond St., W. C. 1, London.
Place: Windermere. Time: Between Easter and Whitsunday.

Canadian Paediatric Society

President: Dr. D. B. Leitch, 210 McLeod Bldg., Edmonton, Al.
Secretary: Dr. R. L. Denton, 1615 Cedar Ave., Montreal 25.

Danish Pediatric Society

President: Dr. A. Rothe-Meyer, Children's Hospital Fûglebakken, Copenhagen F.
Secretary: Dr. E. Winge Flensborg, Children's Hospital Mantinsvej, Copenhagen V.
Place: Different hospitals. Time: First Wednesday of every month.

*Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Departmento de Pediatria da Associação Paulista de Medicina

President: Dr. Oswaldo Riedel de Souza e Silva.
Secretaries: Dr. Ovidio Collesi.
Dr. Helda Elina Vieira de Barros.
Place: Avenida Brigadeiro Luiz Antonio, 278, São Paulo, Brasil.

Deutsche Gesellschaft für Kinderheilkunde

President: Prof. Dr. Adam, Universitats Kinderklinik, Erlangen.
Secretary: Prof. Dr. Jochims, Städtische Kinderklinik, Lübeck.
Place: Bayreuth. Time: Sept. 1-4, 1952.

Hellenic Society of Pediatrics

President: Dr. Spiros Charocopos, Alexandras Ave. 1, Athens.
Secretary: Dr. Nikas Zervos.
Place: Amphitheater, Medical School of the University of Athens. Time: Once a month.

Nederlandse Vereniging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Norsk Pediatrisk Selskap

President: Dr. Arne Njå, Sporveisgt. 29, Oslo.
Secretary: Dr. Helge Granrud, Abbedikollen 38, Bestun, Oslo.
Place: Barneklinikken, Rikshospitalet, Oslo. Time: Friday, six times a year.

Pediatric Society of New Zealand

President: Dr. Edward J. Cronin, Power Board Bldg., Queen St., Auckland.
Secretary: Dr. J. D. Matthews, 104 Symonds St., Auckland.
Place: Auckland. Time: Sept. 9, 1952.

Philippine Pediatric Society

President: Dr. Renato Ma. Guerrero.
Secretary: Dr. Felix A. Estrada.
Place: Santo Tomas University Hospital and other pediatric centers. Time: Every two months.

Royal Society of Medicine, Section of Paediatrics

President: Dr. D. W. Winnicott.
Secretary: Dr. J. J. Kempton; Dr. A. P. Norman.
Sectional Editor: Dr. D. MacCarthy
Place: 1 Wimpole St., London W.1. Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft für Pädiatrie

President: P. D. Dr. F. Bamatter, St.-Léger 8, Genève.
Secretary: Dr. M. Nicod, Place Bel-Air 2, Lausanne.

Sociedad Argentinade Pediatrie

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

Sociedad Boliviano de Pediatria

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S. C. I. S. P. Bldg. **Time:** Every Thursday.

Sociedade Brasiliera de Pediatria

For officers, see IV° Congreso Sudamericano de Pediatria, above.

Sociedad Chihuahuense de Pediatría

President: Dr. Alfonso Ruiz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., México.

Sociedad Chilena de Pediatria

President: Prof. Dr. Raúl Gantes A.
Secretary General: Dr. Edmundo Cardemil.
Place: Medical Society, Merced 565, Santiago.

Sociedad Colombiana de Pediatria

President: Dr. Jorge Camacho Gamba.
Vice-President: Dr. Antonio Alvarez Riaño.
Secretary: Dr. Hernando Vanegas A.
Treasurer: Dr. Efrain Perry Villate.

Sociedad Cubana De Pediatria

President: Prof. Agustin Castellanos y Gonzales.
Secretary: Dr. Carlos Hernandez Miyares, Apartado 2430, Habana.
Place: Catedra de Clinica Infantil Hospital Nuestra Senora de las Mercedes and Hospital Municipal de Infancia, Habana. **Time:** 9 p.m., last Wednesday of every month.

Sociedad de Pediatría de Concepción (Chile)

President: Dr. Próspero Arriagada.
Secretary: Dr. Guillermo Repetto D.
Place: Hospital Clinico Reginal Concepción. **Time:** 7:30 p.m., second Tuesday of every month, April to December, inclusive.

Sociedad de Pediatria del Litord

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary General: Dr. Elsa Galimany.

Sociedad de Pediatria y Puericultura del Atlantico

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Teasurer: Dr. Hernando Borrios Angulo.

Sociedade Portugesa de Pediatria

President: Prof. Dr. Lucio de Almeida.
Vice-President: Dr. Cordeiro Ferreira.
Secretary General: Prof. Dr. Carlos Salazar de Sousa.
Treasurer: Dr. Mario Cordeiro.
Place: Clinica pediatrica do Hospital D. Estefania, Lisbon. Time: Monthly.

Sociedad Uruguaya de Pediatria

President: Dr. Euclides Peluffo.
Secretary: Dr. Ruben Gorlero Bacigalupi.
Place: Av. Agraciada 1464, piso 13, Montevideo.

Sociedad Venezolana de Puericultura y Pediatría

President: Dr. Guillermo Rangel.
Secretary: Dr. Guillermo Tovar E., P.O. Box 5, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

Sociedad Yucateca de Pediatria

President: Dr. Humberto Perez Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

La Société de Pédiatrie de Montréal

President: Dr. Henri Charbonneau, 3095 Sherbrooke, Montréal.
Secretary: Dr. Edmond Baril, 301 Carré St-Louis, Apt. 1, Montréal.
Time: Second Thursday of each month.

Société de Pédiatrie de Paris

President: Prof. Jean Cathala, 45 rue Scheffer, Paris XVI.
Secretary: Prof. Maurice Lamy, 94 rue de Varenne, Paris VII.
Place: Hôpital des Enfants Malades, 149 rue de Sèvres, Paris XV. Time: 4 p.m., third Tuesday of each month.

Société de Pédiatrie de Québec

President: Dr. Roland Thibaudeau, 203 des Erables, Québec.
Secretary: Dr. Euclide Dechêne, 312 du Roi, Québec.
Place: Quebec. Time: May and November.

South African Paediatric Association

Chairman: Dr. Seymour Heymann, 904 Medical Center, Jeppe St., Johannesburg.
Secretary-Treasurer: Dr. I. Kessel, Transvaal Memorial Hospital for Children, Milner Park, Johannesburg.

Swedish Association of Pediatrics

President: Prof. Sture Siwe, Lund.
Secretary: Dr. Karl-Axel Melin, Färjestadsvägen 16, Bromma.

Swedish Medical Society, Section for Pediatrics and School Hygiene

President: Docent Urban Hjarne, Stockholm.
Secretary: Dr. M. d'Avignon, Pediatric Clinic, Karolinska Sjukhuset, Stockholm 60.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm, and Pediatric Clinic, Upsala. Time: Second Friday of each month, except summer.

UNITED STATES

National

American Medical Association, Section on Pediatrics

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. Wyman C. C. Cole, 3001 W. Grand Blvd., Detroit.

American Academy of Pediatrics

President: Dr. Warren W. Quillian, 140 Alhambra Circle, Coral Gables, Miami 34, Fla.
Secretary: Dr. E. H. Christopherson, 636 Church St., Evanston, Ill:
Place: Palmer House, Chicago. Time: Oct. 20-23, 1952.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Horace Hodes.

Secretary: Dr. Sydney S. Gellis.

THE AMERICAN PEDIATRIC SOCIETY

President: Dr. Irvine McQuarrie, University of Minnesota Hospitals, Minneapolis.

Secretary: Dr. Aims C. McGuinness, 237 Medical Laboratories, University of Pennsylvania, Philadelphia 4.

Place: Hotel Traymore, Atlantic City, N. J.; May 6, 7, and 8, 1953.

Sectional

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. John T. Mason.

Secretary: Dr. Stanley R. Child.

Place: Ambassador Athletic Club, Salt Lake City. Time: 7 p.m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Albert W. Fellows.

Secretary: Dr. Harry Shwachman, 300 Longwood Ave., Boston.

Place: Boston, except Spring meeting. Time: Wednesdays, four times a year.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Carl Ashley, 2455 N. W. Marshall St., Portland, Ore.

Secretary-Treasurer: Dr. S. Gorham Babson, 1107 S. W. 13th St., Portland, Ore.

Place: Sun Valley, Idaho (1952), Seattle (1953). Time: September, 1952, and March, 1953.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. F. G. Hedenstrom, 420 Lowry Medical Arts Bldg., St. Paul.

Secretary: Dr. Charles L. Steinberg, 1118 Lowry Medical Arts Bldg., St. Paul.

Place: Minneapolis; St. Paul; Duluth, Minn., and Rochester, Minn. Time: January, April, July, and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. John Lichty, Pediatric Department, Colorado General Hospital, 4200 E. 9th Ave., Denver.

Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.

Place: Announced by mail. Time: Monthly dinner meetings, October to June.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.

Secretary: Dr. Carl A. Erickson, 960 E. Green St., Pasadena, Calif.

Place: Jonathan Club of Los Angeles. Time: 6:30 p.m., second Wednesday in January, March, May, September, and November.

State

ALABAMA PEDIATRIC SOCIETY

President: Dr. David B. Monsky, 748 Adams St., Montgomery 5.

Secretary: Dr. Alice H. Pye, 305 Church St., Montgomery.

Place: Montgomery.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Henry E. Running.

Secretary: Dr. William F. Schaffman.

Time: On Call.

California Medical Association, Section on Pediatrics

Chairman: Dr. Joseph W. St. Geme, 511 S. Bonnie Brae, Los Angeles 5.
Secretary: Dr. Alvin H. Jacobs, 2201 Webster St., San Francisco 15.
Assistant Secretary: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills.

Florida State Pediatric Society

President: Dr. Charlotte C. Maguire, 1413 Kuhl Ave., Maguire Bldg., Orlando.
Secretary-Treasurer: Dr. Wesley S. Nock, 273 Alhambra Circle, Coral Gables.
Place: West Palm Beach. Time: Nov. 8 and 9, 1952.

Georgia Pediatric Society

President: Dr. John A. Simpson, Athens.
Secretary: Dr. J. Harry Lange, 490 Peachtree St., Atlanta.
Place: Savannah. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Joseph Hetzel, 51 Central Ave., Waterbury.
Secretary: Dr. James H. Root Jr., 103 N. Main St., Waterbury.
Time: With the Connecticut State Medical Society in the spring, with the Connecticut State Clinical Congress in the fall; winter meeting usually in December.

Illinois State Medical Society, Section on Pediatrics

Chairman: Howard R. Miller, 418 Jefferson Bldg., Peoria 2.
Secretary: Harry H. Boyle, 2376 E. 71st St., Chicago 49.

Indiana State Pediatric Society

President: Dr. Harold D. Lynch, Evansville.
Secretary: Dr. L. T. Meiks, Indianapolis.

Iowa Pediatric Society

President: Dr. John McKitterick, 315 Tama Bldg., Burlington.
Secretary: Dr. James Dunn, 501 Davenport Bank Bldg., Davenport.

Massachusetts Hospital Association

President: Dr. Philip D. Bonnet, Administrator, Massachusetts Memorial Hospitals, Boston.
Executive Secretary: Henry G. Brickman, 14 Somerset St., Boston 8.
Place: Boston. Time: Annual Meeting, January, 1953.

Michigan State Medical Society, Pediatric Section

President: Dr. Horace L. French, 301 Seymour Ave., Lansing.
Secretary: Dr. Park S. Bradshaw, 1014 Jefferson St., Muskegon.
Place: Detroit: Time: September, 1952.

Montana Pediatric Society

President: Dr. Orville M. Moore, 555 Fuller Ave., Helena.
Secretary: Dr. Joseph W. Brinkley, 410 Central Ave., Great Falls.
Place: Variable. Time: Spring and fall.

Nebraska Pediatric Society

President: Dr. Michael Crofoot.
Vice-President: Dr. Donald C. Nilsson.
Secretary-Treasurer: Dr. A. J. Lombardo, 401 Aquila Ct., Omaha.
Place: Children's Memorial Hospital. Time: 6 p.m., dinner, third Thursday of each month.

New Hampshire Pediatric Society

President: Dr. Douglass W. Walker, Laconia.
Secretary: Dr. Wm. D. Penhale, Concord.
Place. Alternately Concord, Hanover, Laconia, and Manchester. Time: Four times a year.

New Mexico Pediatrics Society

President: Dr. M. K. Wylder, Suite 14, Medical Arts Sq., Albuquerque.
Secretary: Dr. Ly Werner, Suite 25, Medical Arts Sq., Albuquerque.
Place: Variable. Time: Every two or three months.

North Carolina Pediatric Society

President: Dr. J. A. Shaw, 107 Bradford Ave., Fayettesville.
Secretary: Dr. Bailey Webb, 809 W. Chapel Hill St., Durham.
Place: Pinehurst. Time: May 6, 1952.

South Carolina Pediatric Society

President: Dr. Walter Moore Hart, 117 W. Cheves St., Florence.
Secretary: Dr. John R. Paul Jr., 82 Rutledge Ave., Charleston.
Place: Columbia, S. C. Time: Second Monday and Tuesday in September; Sept. 8 and 9, 1952.

Tennessee Pediatric Society

President: Dr. O. L. Von Canon, 846 McCallie Ave., Chattanooga.
Secretary: Dr. Oliver W. Hill, 4807 Newcom Ave., Knoxville.

Texas Pediatric Society

President: J. A. Bybee, Beaumont.
President-Elect: Dr. Robert L. Moore, Dallas.
Secretary: Dr. M. C. Carlisle, 1410 Austin Ave., Waco.
Treasurer: Dr. Jack M. Woodall, Big Springs.
Place: Dallas. Time: Oct. 17 and 18, 1952.

Virginia Pediatric Society

President: Dr. Edwin L. Kendig Jr.
Secretary: Dr. T. J. Humphries.

Wisconsin State Medical Society

Chairman: Dr. N. L. Low, Racine
Vice-Chairman: Dr. E. H. Pawsat, Fond du Lac.
Secretary: Dr. Samuel E. Kohn, Milwaukee.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave., Cleveland 12.
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p.m., October, December. February, and March.

Baltimore City Medical Society, Pediatric Section

President: Dr. Wilson Grubb, 4 E. 33d St., Baltimore 18.
Secretary: Dr. Gibson J. Wells, 3101 St. Paul St., Baltimore 18.
Place: 1211 Cathedral St., Baltimore 1. Time: 8:30 p.m., second Tuesday in November, January, and March.

Bronx Pediatric Society

President: Dr. M. H. Grand, 1749 Grand Concourse, New York.

Secretary: Dr. Charles T. Fried, 1220 Grand Concourse, New York.

Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August, and September.

Brooklyn Academy of Pediatrics

President: Dr. Stanley S. Lamm, 20 Plaza St., Brooklyn.

Secretary: Dr. Henry Cohen, 1761 E. 19th St., Brooklyn.

Place: Granada Hotel, Brooklyn. Time: 8:45 p.m., fourth Wednesday of February, March, April, October, and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold.

Secretary: Dr. Richard A. Downey.

Place: Children's Hospital, 219 Bryant St. Time: 8:30 p.m., first Monday of each month, September to June.

Central New York Pediatric Club

President: Dr. Frank Williams, 58 Swan St. S., Albany.

Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester.

Place: Various cities in New York State; fall meeting jointly with Upper New York State Academy of Pediatrics. Time: Third Tuesday of April and October.

Central Ohio Pediatric Society

President: Dr. E. V. Turner, 2479 E. Main St., Columbus.

Secretary: Dr. James Beasley, Lancaster.

Place: As announced. Time: Third Wednesday of September, November, January, March, and May.

Chicago Pediatric Society

President: Dr. George F. Munns.

Secretary: Dr. Matthew M. Steiner.

Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. Nicholas M. Kotona, 5771 Glenway Ave., Cincinnati 38.

Secretary: Dr. John E. Allen, 2546 Auburn Ave., Cincinnati 19.

Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dade County Pediatric Society

President: Dr. Lynn Whelchel, DuPont Bldg., Miami, Fla.

Secretary: Dr. Howard Engle, 311 Lincoln Rd., Miami Beach, Fla.

Dallas Pediatric Society

President: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas.

Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave., Dallas.

Place: Children's Hospital of Texas. Time: 6:30 p. m., first Thursday in each month.

Detroit Pediatric Society

President: Dr. Ruben Meyer, 938 Maccabees Bldg., Detroit.

Secretary: Dr. W. W. Zuelzer, Children's Hospital of Michigan, Detroit.

Place: Variable. Time: Five times a year.

Honolulu County Pediatric Society

President: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu.

Corresponding Secretary and Treasurer: Dr. John H. Peyton, Kauikeolani Children's Hospital, Honolulu.

Honolulu Pediatric Society

President: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu.

Recording Secretary: Dr. M. H. Hasegawa.

Corresponding Secretary: Dr. John Peyton, Kauikeolani Children's Hospital, Honolulu.

Place: At doctors' homes in rotation. Time: 6 p.m., third Thursday of each month.

Houston Pediatric Society

President: Dr. Emanuel B. Brandes, 3101 Fannin St., Houston.

Secretary: Dr. Robert D. Lomas, 5101 Fannin St., Houston.

Place: River Oaks Country Club. Time: 7:30 p.m., fourth Tuesday of each month.

Kansas City Southwest Pediatric Society

President: Dr. Frank Hogue, Plaza Medical Bldg., Kansas City, Mo.

Secretary: Dr. S. J. Kranson, Truman Rd. and Ash, Independence, Mo.

Place: University Club, Kansas City, Mo. Time: On call.

Long Beach Pediatric Society

President: Dr. Kenneth Berkaw, 211 Cherry Ave., Long Beach, Calif.

Secretary: Dr. C. W. Latshaw, 3821 Atlantic Ave., Long Beach, Calif.

Place: Victor Hugo Restaurant, 730 E. Broadway. Time: First Tuesday night of every month.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Sidney Rosin, 6230 Wilshire Blvd., Los Angeles.

Secretary: Dr. Arthur J. Holmes, 65 N. Madison Ave., Pasadena 1.

Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd., Los Angeles. Time: Second Thursday of alternate months beginning in September.

Louisville Pediatric Society

President: Dr. Lee Palmer.

Secretary: Dr. Martin Z. Kaplan.

Place: Variable. Time: Five times a year.

Medical Society of the County of Kings and Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Max Palinsky, 1270 45th St., Brooklyn 19.

Secretary: Dr. Bernard Greenberg, 670 Ocean Ave., Brooklyn 26.

Place: Kings County Medical Society Auditorium, 1313 Bedford Ave., Brooklyn. Time: 9 p.m., fourth Monday of January, March, April, October, and November.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington 20.

Secretary: Dr. John E. Cassidy, 5402 Connecticut Ave. N.W., Washington.

Place: Medical Society Bldg., 1718 M St. N.W., Washington. Time: Spring and fall.

Memphis Pediatric Society

President: Dr. James G. Hughes, 20 S. Dunlap, Memphis.

Secretary: Dr. George S. Lovejoy, 609 N. Highland, Memphis.

Place: Rotated among four hospitals. Time: 7:30 p.m., second Tuesday of each month.

Milwaukee Pediatric Society

President: Dr. Franklin Mellencamp, 1513 E. Capitol Dr., Milwaukee.

Secretary: Dr. Karl Beck, 1411 Wauwatosa Ave., Milwaukee.

Place: Milwaukee University Club. Time: Second Wednesday of February, April, June, and October.

Mobile Pediatric Society

President: Dr. Daniel Sullivan, 1420 Government St., Mobile, Ala.

Secretary: Dr. Robert O. Harris III, 1514 Government St., Mobile, Ala.

Place: Admiral Semmes Hotel. Time: 7:30 p.m., fourth Thursday of September, November, January, March, and May.

Nashville Pediatric Society

President: Dr. Thomas Weaver, Bennie Dillon Bldg., Nashville, Tenn.

Secretary: Dr. Ethel Walker, 3415 West End Ave., Nashville, Tenn.

Place: Homes of members. Time: Third Thursday of every month.

Nassau Pediatric Society

President: Dr. Daniel Blitz, 1 Club Drive, Woodmere, N. Y.

Secretary-Treasurer: Dr. David J. Posner, 98 Wolcott Rd., Levittown, N. Y.

Place: Garden City Hotel, Garden City, L. I., N. Y. Time: 7:30 p. m., second Monday of October, December, February, April, and June.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Jerome L. Kohn, 50 W. 96th St., New York 25.

Secretary: Dr. Lawrence B. Slobody, 1 E. 105th St., New York 12.

Place: New York Academy of Medicine, 2 E. 103d St. Time: 8:30 p.m., second Thursday of each month, November to May, inclusive.

Northern California Pediatric Society

President: Dr. John A. Anderson, Stanford Hospital, 2351 Clay St., San Francisco 15.

Secretary: Dr. Edward Campion, 1018 E St., San Rafael.

Place: San Francisco. Time: Quarterly, as speakers are available.

Oklahoma City Pediatric Society

President: Dr. C. M. Bielstein, 301 N.W. 12th St., Oklahoma City.

Secretary: Dr. Louis Frank, 1200 N. Walker St., Oklahoma City.

Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. John B. Bartram, 2600 Lawrence St., Philadelphia 33.

Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.

Place: College of Physicians, 19 S. 22d St. Time: 8:30 p.m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. Christian John Stoecklein, 519 Medical Arts Bldg., Pittsburgh 13.

Secretary-Treasurer: Dr. James W. Stirling, 694 Lincoln Ave., Pittsburgh 2.

Place: Western State Psychiatric Institute and Clinic. Time: Second Friday in October, December, February, and April.

Queens Pediatric Society

President: Dr. Samuel Dillon, 119-20 Rockaway Beach Blvd., Rockaway Park, N. Y.

Secretary: Dr. Moe Goldstein, 111-32 76th Ave., Forest Hills, N. Y.

Place: Seminole Club, 112th St. and 70th Rd., Forest Hills, N. Y. Time: Second Tuesday in October, December, February, and April.

Richmond Pediatric Society

President: Dr. Hobart T. Dougan, 1832 Monument Ave., Richmond 20, Va.

Secretary: Dr. Robert A. Hoffman, 1001 W. Franklin St., Richmond 20, Va.

Place: Medical College Hospital. Time: 8 p.m., third Thursday of each month, except June, July, and August.

San Antonio Pediatric Society

President: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.

Secretary: Dr. Virginia S. Stovall, 1116 S. Texas Bldg., San Antonio 5.

Time: 7:30 p. m., supper, first Tuesday of each month.

Seattle Pediatric Society

President: Dr. O. William Anderson.

President-Elect: Dr. Robert Tidwell.

Secretary-Treasurer: Dr. James L. Tucker.

Place: College Club. Time: 6:30 p.m., fourth Friday of each month from September to June.

St. Louis Pediatric Society

President: Dr. Maurice J. Lonsway.

Secretary: Dr. John C. Herweg.

Place: Candlelight House, 7800 Clayton Rd. Time: 6:30 p.m., second Thursday of each month from October to May, inclusive.

Santa Barbara Pediatric Society

President: Dr. Clarence B. Hills, 22B. W. Micheltorena St., Santa Barbara, Calif.

Secretary: Dr. Louise P. Brown, 3017 Foothill Rd., Santa Barbara, Calif.

Place: Varies. Time: Two to three times yearly, on call.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Fred J. Chapin, 101 John St., Bay City.

Secretary-Treasurer: Dr. George H. Lowrey, University Hospital, Ann Arbor.

Place: University Hospital, Ann Arbor. Time: October, 1952.

Waco Pediatric Society

President: Dr. J. M. Garrett, 1408 Austin Ave., Waco, Texas.

Secretary: Dr. C. G. Shellenberger, 1318 Austin Ave., Waco, Texas.

Place: 1917 Austin Ave., Waco, Texas. Time: Third Tuesday of each month.

Westchester County Medical Society, Pediatric Section

President: Dr. Herbert Kahan, 650 Main St., New Rochelle, N. Y.

Secretary: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.

Place: The Roger Smith Hotel, White Plains, N. Y. Time: Four dinner meetings a year, November, February, April, and June.

Western Michigan Pediatric Society

President: Dr. A. Morgan Hill, 310 Fulton, E., Grand Rapids.

Secretary: Dr. John C. Montgomery, 1810 Wealthy St., S.E., Grand Rapids.

Place: Two meetings in Grand Rapids, two elsewhere. Time: First Wednesday of October. November, April, and May.

Wichita Pediatric Society

President: Dr. Frank L. Menehan.

Secretary: Dr. R. C. Knappenberger.

Place: Homes of members. Time: 8:30 p. m., first Thursday, October through May.

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1. Booher, C. E., et al.: J. Pediat. *38*:411 (April) 1951.
2. Yow, E. M., et al.: Am. Pract. *2*:689 (Aug.) 1951.
3. Potterfield, T. G., and Starkweather, G. A.: J. Philadelphia Gen. Hosp. *2*:6 (Jan.) 1951.
4. Graves, F. B., and Ball, W. O.: J. Pediat. *39*:135 (Aug.) 1951.

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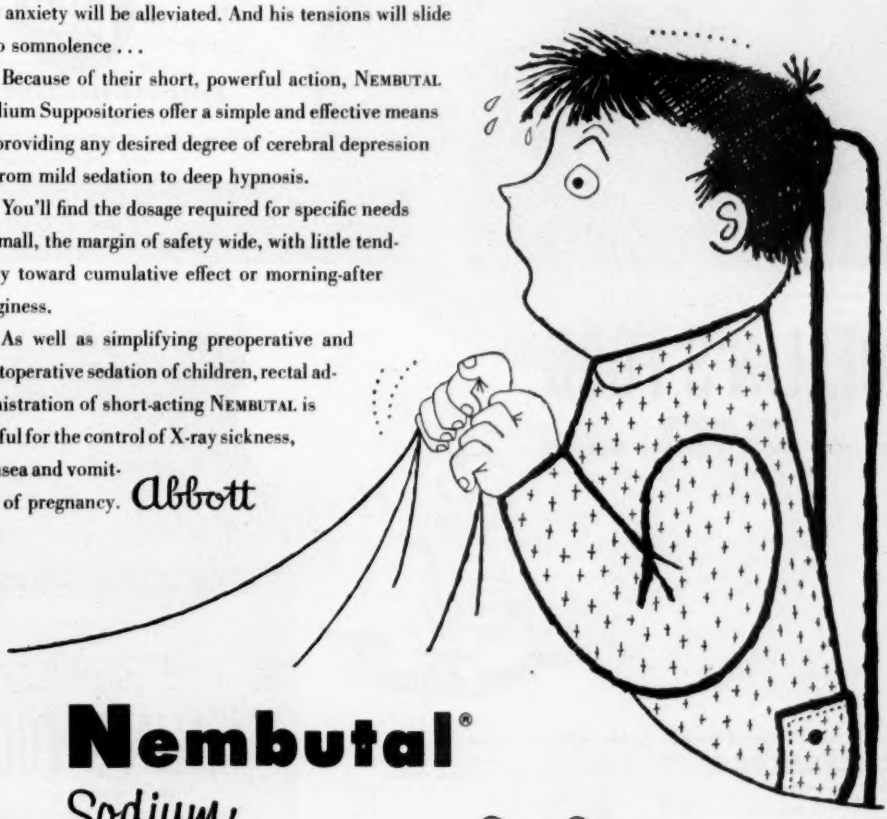

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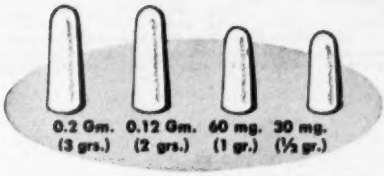

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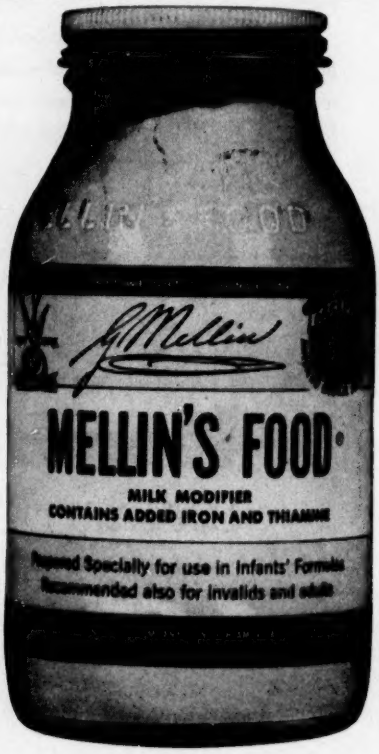
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Bibliography:

1. Frank, P.F., Wilcox, C., and Finland, M.: In Vitro Sensitivity of Coliform Bacilli to Seven Antibiotics, J. Lab. & Clin. Med. *35*:188 and 205, 1950.
2. Jawetz, E. and Coleman, V.R.: Laboratory and Clinical Observations on Aerosporin (Polymyxin B), J. Lab. & Clin. Med. *34*:751, 1949.
3. Pulaski, E.J. and Rosenberg, M.L.: Use of Polymyxin in Gram Negative Urinary Tract Infections, J. Urol. *62*:564, 1949.
4. Kagan, B.M., et al.: Polymyxin B and Polymyxin E, J. Lab. & Clin. Med. *37*:402, 1951.
5. Lieberman, D. and Jawetz, E.: Treatment of Chronic Shigella Infections in Children with Oral Polymyxins, Pediatrics *18*:249, 1951.
6. Jawetz, E.: Infections with Pseudomonas aeruginosa Treated with Polymyxin B, Arch. Int. Med. *89*:90, 1952.

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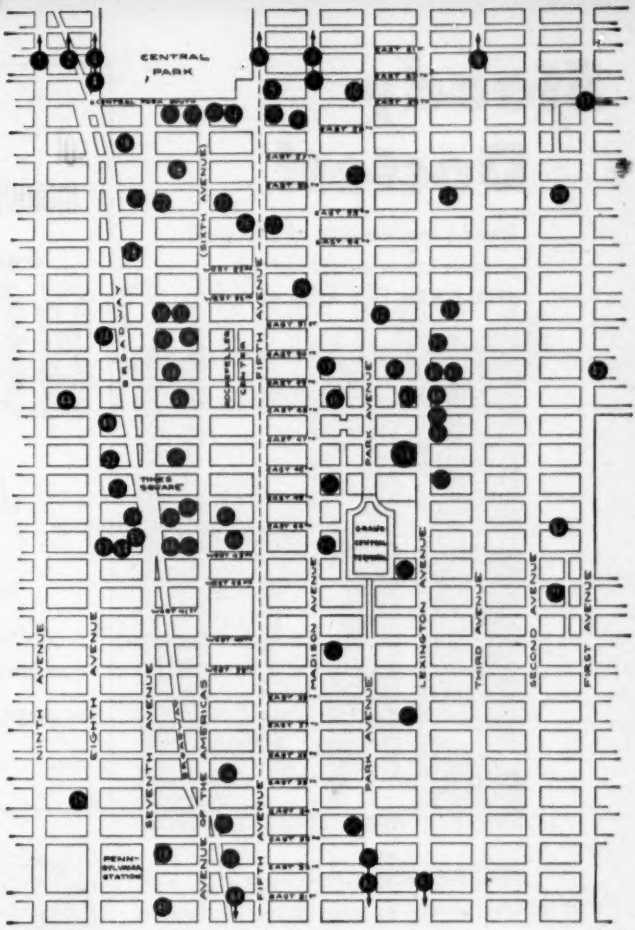

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